Manuscript Details

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Title	Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal meta-analysis.
Article type	Review Article

Abstract

Objectives: To conduct a systematic review and longitudinal meta-analysis of early rheumatoid arthritis (RA) cohorts with long-term data on pain, fatigue or mental well-being. Methods: Searches using PUBMED, EMBASE and PyscInfo were performed to identify all early RA cohorts with longitudinal measures of pain, fatigue or mental well-being, along with clinical measures. Using longitudinal meta-analyses, the progression of each outcome over the first 60-months was estimated. Cohorts were stratified based on the median recruitment year to investigate secular trends in disease progression. Results: Of 7,319 papers identified, 75 met the inclusion criteria and 46 cohorts from 41 publications provided sufficient data on 18,046 patients for meta-analysis. The Disease Activity Scores (DAS28) and the Short-Form 36 (SF-36) Physical Component Score (PCS) indicated that post-2002 cohorts had statistically significant improvements over the first 60-months compared to pre-2002 cohorts, with standardised mean differences (SMD) of 0.86 (95% Confidence Intervals 0.34 to 1.37) and 0.76 (95% CI 0.25 to 1.27) respectively at month-60. However, post-2002 cohorts indicated statistically non-significant improvements in pain, fatigue, functional disability and SF-36 Mental Component Score (MCS) compared to pre-2002 cohorts, with SMD of 0.24 (95% CI -0.25 to 0.74), 0.38 (95% CI -0.11 to 0.88), 0.34 (95% CI -0.15-0.84) and -0.08 (95% CI -0.41 to 0.58) at month-60 respectively. Conclusions: Recent cohorts indicate improved levels of disease activity and physical quality of life, however this has not translated into similar improvements in levels of pain, fatigue and functional disability by 60-months.

Taxonomy	Adverse Effect of Pain, Cohort Study, Systematic Review with Meta-Analysis, Fatigue, Quality of Life, Autoimmune Disorder
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Submission Files Included in this PDF

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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

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Seminars in Arthritis and Rheumatism
Editor in Chief: Marc Hochberg

Dear Prof Marc Hochberg,

Article Type: Systematic Review with Meta-analysis
Submission of Manuscript: Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal meta-analysis.

Carpenter, L.[1], Barnett, R.[1], Mahendran, P.[1], Nikiphorou, E.[2], Gwinnutt, J.[3], Verstappen, S.[3], Scott, D.L.[2] & Norton, S.[1,2]
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Thank you for considering the following manuscript for publication in *Seminars in Arthritis and Rheumatism.* The paper documents a systematic review of all early Rheumatoid Arthritis (RA) cohorts with longitudinal summary data on pain, fatigue or mental well-being, along with disease activity and functional disability.

The aim of the review was to investigate the long-term trajectory of patient reported outcomes (pain, fatigue and mental well-being) in patients diagnosed with early RA at different periods over the last 30-years and establish whether advances in the treatment of RA have led to improvements in these patient reported measures. This was achieved using longitudinal meta-analytic techniques rarely seen in the medical literature.

In total, 46 cohorts from 41 published studies were identified, contributing a total of 18,046 patients, with longitudinal data. Of those, 29 cohorts provided sufficient data on 10,132 patients on the outcomes of interest for meta-analysis.

The systematic review was conducted by LC, RB and PM, analysis and manuscript preparation were performed by LC and SN, and drafts of the manuscript where reviewed and modified by EN, JG, SV and DLS. Sam Norton is a Fellow of MQ: Transforming Mental Health and Arthritis Research UK (MQ16IP18). Lewis Carpenter time is fully supported by MQ16IP18. Prof David L Scott's time is funded by a NIHR Programme grant (RP-PG-0610- 10066).

Sincerely,

Dr Lewis Carpenter

Comments from the editors and reviewers:
-Reviewer 1
The authors have endeavored to address the reviewers' comments effectively. At the same time, it remains the case that joint counts, which are components of DAS28, are more likely to improve with placebo than self-report measures (1)(one of the authors of that reference is an author of this manuscript), apparently on the basis of bias on the part of physicians and study coordinators.

The disclaimer about different numbers of joints in different studies is somewhat legitimate, but could be addressed in part as percent of maximum for any joint count, although that approach may be limited by the fact that certain joints are more likely to be affected than others.

Also, there appears a somewhat excessive emphasis on p values, reflected in a comment that a difference "did not reach statistical significance." Many clinically important differences may not have a P value <0.5, and many p values <0.5 are not clinically important. The authors might review the manuscript to deemphasize p values, although they may choose to ignore this suggestion.

1. Strand V, Cohen S, Crawford B, Smolen JS, Scott DL, Leflunomide Investigators G. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology (Oxford). 2004;43(5):640-7.

Response: We thank the reviewer for highlighting just how important this aspect of the manuscript is. We have to conduct the additional analysis using the data available to shed light on this issue in the review. It was not feasible to email all the authors to request the data where it was not reported in the manuscript, therefore a sensitivity analysis was conducted using the data that was readily reported on not only the joint counts, but also acute phase markers.

We have provided this additional analysis as part of the supplementary material and alluded to this analysis in the 'Sensitivity Analysis" section of the results:

"Additional analysis investigated the progression of the sub-components of the DAS28; the Swollen Joint Count (SJC), Tender Joint Count (TJC), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), in a sub-group of cohorts reporting this data. Of the 37 cohorts with DAS28 data, 25 had data on SJC, 23 on TJC, 22 on CRP and 18 on ESR. Whilst SJCs, TJCs and CRP showed greater declines in post-2002 compared to pre-2002 cohorts, the estimates over the follow-up periods were inconclusive due to low levels of data over the follow-up. Details of this sub-analysis are presented in the supplementary material."

Reviewer 2

- The authors carried out an impressive study and were responsive to the reviewers' comments and suggestions. I have just one minor question about the longitudinal statistical analysis. In the longitudinal analysis, it appears that the authors performed a hierarchical meta-regression, to investigate heterogeneity while accounting for the fact that a study can contribute estimates at multiple time points. That is, a hierarchical version of this:
https://handbook-5-1.cochrane.org/chapter_9/9_6_4_meta_regression.htm

If that is accurate, then I recommend using the meta-regression language somewhere when describing the method.

Response: We thank the reviewers for the positive remarks on the paper and we are pleased that our responses were well received. We agree with the minor comment raised, and have included the following statement in the statistical analysis section of the manuscript to aid clarity of the methods used:

“This is similar to meta-regression techniques, which assess the effect of covariates on the study level estimates.”

As an additional note, it was apparent to the authors that statistics about the number of cohorts and studies included in the review were those used in an earlier version of the manuscript. We apologise for this error, but have made very minor corrections to the Abstract, Figure 1 and the second paragraph of the Results section describing the number of studies included. Rest assured, this had no effect on the results or conclusions of the paper.

Introduction

Rheumatoid arthritis (RA) is a chronic auto-immune disease that causes inflammation and pain in joints. It is estimated to affect approximately 1% of the UK adult population[1]. Inadequately treated, it can lead to long-term physical damage, namely in the form of bone erosions and joint space narrowing, as well as reduced quality of life. The adoption of biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) in the most severe cases[2], as well as the introduction of the Treat-2-Target (T2T) approach to disease management in the early 2000's[3], which employs the use of early, more aggressive conventional DMARD (csDMARD) therapies[4] have had a large impact on reducing inflammation and radiographic joint damage in recent years[5–7]. Despite this, there is little indication that this has translated into equivalently large, clinically-meaningful improvements in pain, fatigue and health related quality of life (HRQoL)[8–11]. This is of particular importance in RA populations, as there is evidence that patients with RA have higher prevalence of psychological distress, such as depression and anxiety[12–15] compared to the general population and that those patients with persistent depression have been evidenced to respond less well to bDMARD therapies[16]. Also, patients with RA with worse quality of life outcomes are associated with higher Health Care Resource Utilisation (HCRU)[17].

There is a sparsity of systematic reviews, including meta-analysis of quantitative data, investigating HRQoL outcomes. Matcham et al.[14] is one of the few published systematic reviews to investigate HRQoL in observational trials of RA populations, and demonstrated that HRQoL was lower in patients with RA when compared to other chronic conditions, such as Type 2 diabetes and congestive heart failure. However, much of the data presented were cross-sectional in nature, and as such does not document how HRQoL progresses over time, or indeed how modern approaches to treatment and management may have impacted on disease progression over different periods. To our knowledge, only one other review explored HRQoL in older patients with RA (≥75 years) and found that pain, increased age and increased functional disability all contributed to worse HRQoL[18].

The aim of this systematic review was to examine symptom severity and HRQoL at different points during the RA disease course and assess whether there have been changes in symptom levels and HRQoL over the last 30 years, in light of the substantial changes in treatment strategies over the last few decades.

Methods

Identifying publications

A systematic search of 3 databases, namely PubMed, EMBASE and PsycInfo, was conducted between 1975-2017. The search strategy used key words and MeSH terms on the title/abstract and full text as appropriate (See supplementary material for search terms used). Additional lateral search techniques included checking reference lists, performing key word searches in Google Scholar and using the 'cited by' option in PubMed. The review included all studies of adult patients (>18 years old) with early RA, where baseline assessment was <3 years from symptom onset. Diagnosis was confirmed by either the 1987 or 2010 American College of Rheumatology (ACR) criteria. As a systematic review of non-randomised observational cohorts, there was no intervention or comparator group of interest in this review.

Outcome(s)

The outcomes of interest were pain, fatigue and mental wellbeing. Pain and fatigue are typically measured using a Visual Analogue Scale (VAS), however other measures were eligible to be included. Mental health included any measures of quality of life, such as the EuroQol 5-Dimensions (EQ-5D) or the Short-Form 36 (SF-36). Other measures relating to depression and anxiety were also recorded if reported (e.g. Hospital Anxiety and Depression Scores (HADS) and the Beck Depression Inventory (BDI)).

Secondary outcome measures included clinical measures of disease, namely the Disease Activity Score (DAS) and measures of functional disability, namely the Health Assessment Questionnaire (HAQ).

Inclusion/exclusion criteria

Inclusion criteria to select publications comprised of: (1) included a measure of self-reported pain, fatigue or mental well-being, (2) patients had a diagnosis of rheumatoid arthritis, (3) baseline assessments occurred no later than 3-years from symptom onset, (4) prospective cohort study design, (5) had repeated measures (at least two time points), (6) included human participants, and (7) publications written in English.

Publication screening

One reviewer (RB) screened titles/abstracts identified in searches, using the selection criteria to identify potentially relevant papers. A second reviewer (LC) independently screened the title/abstract of 25% of all publications identified against agreed inclusion criteria. Agreement at the title/abstract stage was achieved in 92% of papers, with disagreements resolved through discussion (e.g. longitudinal data was only available for a subset of patients with established disease, not early disease). Both reviewers (LC & RB) then screened all full texts to establish the final set of studies to include in the review. Of the 1,736 full texts screened, agreement was achieved for 99.7% of papers.

Data extraction

Three reviewers (LC, RB and PM) extracted data using a pre-designed form, piloted to ensure all data necessary were captured. It included: cohort name, country of study population, pain/fatigue/mental well-being mean scores and Standard Deviation (SD), along with the outcome measure(s) used, number of patients included, years of recruitment, length of follow-up, proportion of females in the cohort, mean age of patients in the cohort, functional disability mean scores and SD at each recorded follow-up, Disease Activity Score mean and SD at each recorded follow-up (where this was recorded using the DAS44 method, a conversion formula was applied to convert it to DAS28[19]), proportion of patients in the cohort on DMARDS at baseline, proportion of patients in the cohort who were Rheumatoid Factor (RF) positive at baseline and number of patients at each follow-up. In cases where the raw data were not given in the published paper the author(s) were individually contacted to provide this data (n=39).

Quality Assessment

Studies were rated using the Downs and Blacks instrument for non-randomised studies of health care interventions[20]. Since the studies did not examine clinical effectiveness, checklist items related to comparative groups (e.g. randomisation and blinding procedures) were omitted. One reviewer (LC) scored all studies using the amended checklist and another reviewer (PM) independently scored 50% of studies drawn at random. Discrepancies between reviewers were discussed and consensus achieved.

Statistical Analysis

The systematic review extracted data at baseline, and all recorded follow-ups, for a range of different outcomes measuring disease activity, functional disability, pain, fatigue and mental well-being. Whilst traditional meta-analytical methods are used for cross-sectional data, a weighted mixed-effects model was needed to account for the aggregate level summary data of each time point over time. ~~To account for the longitudinal data structure, M~~multivariate meta-analyses were conducted using mixed-effects linear regression models, with a random intercept estimated to account for repeated observations within studies and a random slope for time allowing the rate of progression to vary within studies over time[21]. Since the data are aggregate level for each included cohort at each time point, they were inverse variance weighted using the study level standard error at each recorded time point. Much like a meta-analysis, this allows studies with greater sample sizes to given greater weight in the estimation of the pooled effect estimate. Full Information Maximum Likelihood (FIML) allowed for estimation of time-specific means of every cohort in the event that the data are missing. This is similar to meta-regression techniques, which assess the effect of covariates on the study level estimates. As such, the figures provided represent the estimated pooled mean for that outcome at each follow-up time-point.

Since the cohorts included will be prospective inception cohorts of patients with early RA, it was expected that the progression of all outcomes will be non-linear over time. Previous research has shown how outcomes such as functional disability follow a 'J-Shaped' trajectory in the first years of disease[22], whereby patients initially improve rapidly in the first 12-months following treatment initiation, but then worsen in the subsequent years as disease duration increases. In order to account for this non-linearity, piecewise linear splines were used with a change point at 12-months. This allows for two separate slopes to be estimated by the model, one from baseline to 12-months, and one from 12-months to 60-months. In order to quantify the data from the model, the meta-analysis will be based on the estimated pooled effect for each outcome at four pre-specified time points; baseline, 12-months, 36-months and 60-months.

For each cohort, mid-point between the first and last year of recruitment was used to place the cohorts in chronological order from earliest to latest. Cohorts were then split according to whether the recruitment was pre or post 2002. This has been used in other reviews due to its reflection of the move towards more T2T principles, and also reflects the general median year in early RA cohorts in previous reviews[23]. The dichotomised variable was entered into the mixed effect model, along with an interaction effect with follow-up time. The mean difference between pre and post -2002 cohorts will be used as the main effect estimate. These will be estimated at baseline, 12, 36 and 60-months follow-up for the Pain Visual Analogue Scale (VAS), Fatigue VAS, SF-36 PCS, SF-36 MCS, the HAQ and the DAS

outcomes. Scores <0 indicate more favourable scores for the pre-2002 cohorts, whilst scores >0 indicate more favourable scores for the post-2002 cohort. This will be expressed as both a mean difference, which highlights the change in score relative to the scale in which it was measured, as well as a Standardised Mean Difference (SMD), which allows for direct comparisons between measures with different scales. All analyse were conducted using Stata (ver15) using the 'mixed' command for mixed effects analysis.

Results

A total of 7,319 articles were identified from the 3 databases following the removal of 2,363 duplicates, as shown in Figure 1. Following title and abstract screening, 1,736 full texts were screened for eligibility. In total, 41 articles[11,22,32–41,24,42–51,25,52–61,26,62,27–31] describing data from 46 cohorts where identified, contributing a combined total of 18,046 patients. The median year of recruitment for all cohorts ranged from 1983-2014, with a median year of 2002. Cohorts recruited patients from twenty different countries (Australia[41], Austria[62], Brazil[48], Canada[24,49,53,58], Denmark[28], France[29,32,50], Germany[42,46], Iceland[54], Italy[27,31,56], Japan[35], Latin American[57], The Netherlands[25,34,36,40,59], Norway[33], Scotland[47], South Africa[51], Spain[37,61], Sweden[11,38,60], UK[22,26,39,55], USA[30,43,45,52] and Mexico[44]). The UK had the highest number of cohorts at eight (17%), followed by five (11%) from the Netherlands, and four (9%) from Canada, Sweden and the US. The characteristics of the cohorts, and the patients included in those cohorts are summarised in Table 1.

Table 1 – Summary table of cohort characteristics, and baseline summary statistics of the patients included in the cohorts.

~~However, a~~Although contact was made with ~~the~~ 39 authors for ~~the~~ additional longitudinal data ~~that was required for the meta-analysis~~, only 9 responded~~, leaving a total of 29 cohorts from 25 studies for inclusion in the meta-analysis~~. ~~These cohorts contributed a total of 10,132 patients to the final analyses.~~ With respect to the data collected, 36~~25~~ (78~~86~~%) had ~~longitudinal~~ measures of pain[11,22,33,35,37–40,42,44–46,24,47,49–52,54,56–59,26,61,62,27–32], ~~eight~~813 (28%) had measures of fatigue[26–28,39,44,46,50,52,56], nine~~9~~ (31~~20~~%) had measures of SF-36[26,50,51,55,56,59,60], ~~and~~ 2437 (83~~80~~%) had measures of the HAQ[11,22,34–41,43,44,24,45,47–52,55,56,59,25,61,62,26,28–30,32,33] and 37~~25~~ (80~~6~~%) had measures of DAS[11,22,33–40,42,44,24,45–47,49,50,52,53,55,56,59,26,61,62,27–32]. Alongside SF-36, other longitudinal measures of mental health were also collected, namely the Centre for Epidemiological Studies Depression Scale (CES-D)[49,53,58], The Arthritis Impact Measurement Scale (AIMS)[26] and the Hospital Anxiety and Depression Scale (HADS)[47,63], however the small numbers meant it was not possible to include them in the meta-analysis.

Figure 1 – Prisma Flow Diagram of journal screening process at each stage of the systematic review

Quality Assessment

A modified version of the Down's and Black Checklist was used to assess the quality of each study. Agreement between the two reviewers was high at 99%, and where there were differences, these were resolved through consultation.

Overall, all studies included in the meta-analysis were of high quality, with all studies clearly defining the hypothesis, characteristics of the patients, main findings, and estimates of variability (See supplementary material). The patients included were representative of the general population and there were no indications of 'data dredging'. However, less than 15% of the studies provided characteristics of their patients who were lost to follow-up, and only 20% of the studies appropriately accounted for this loss of follow-up in their analysis.

Whilst >80% of studies were suitably powered, described the principle confounders and appropriately accounted for the longitudinal nature of the study in their analysis, <50% of studies were found to have used appropriate statistical methods and adequately adjusted for all important confounding effects. This was largely due to the reliance on step-wise regression methods, which allow for variable selection but introduce bias in parameter estimates without regularisation[64].

Meta-Analysis

Mean Differences (MD)

The forest plots presented in Figure 2 represent the pooled (model estimated) Mean Differences (MD) between pre and post-2002 cohorts at baseline, 12, 36 and 60-months. For illustration, the sub-group pooled effect estimate for cohorts recruiting patients post-2002 for baseline Pain VAS was 52.48 (95% Confidence Intervals 48.92 to 56.05), whereas the sub-group pooled effect estimate for cohorts recruiting patients post-2002 was 48.32 (95% CI 44.51 to 52.13) (Please see Supplementary Material). This ~~, which~~ equates to a MD of -4.16 (95% CI -9.34 to 1.01), as shown in Figure 2 (allowing for rounding error).

In order to conceptualise the magnitude of the effects, the reported mean differences for each outcome were compared to changes that are deemed clinically important, often referred to as the Minimally Clinically Important Difference (MCID). Whilst thresholds vary, the MCID for pain VAS has been reported to be 11.9[65], whilst estimates for the fatigue VAS have ranged from 8.2 to 11.2 in RA populations[66]. Likewise, the MCID has been reported between 2.5 to 5.0 for the SF-36 PCS and MCS, however studies have demonstrated higher estimates of 7.1 for the SF-36 PCS[67]. As such, an estimate of 8-unit change has been illustrated in Figure 1 for the MCID for the pain, fatigue and SF-36 PCS and MCS. Likewise, a MCID of 0.20 was used for HAQ[65], and 1.00 for the DAS-28[68].

Investigation of the mean differences of all the outcomes between pre- and post-2002 studies indicate that, at baseline, pre-2002 cohorts had marginally lower levels of pain (-4.17; 95% CI -9.34 to 1.01), SF-36 MCS (-5.25; 95% CI -11.74 to 1.23) and HAQ (-0.11; 95% CI -0.27 to 0.06), whilst pre-2002 cohorts had higher levels of fatigue (3.43; 95% CI -1.32 to 8.17), SF-36 PCS (0.70; 95% CI -4.23 to 5.62) and DAS (0.18; 95% CI -0.16 to 0.51) at baseline. However, none of these differences reached statistical significance (See Figure 2~~1~~).

By ~~the~~ 12-months, all outcomes exhibit an improvement in scores. However, there is variation in the magnitude of this improvement in pre- and post-2002 cohorts for each outcome. With the SF-36 PCS there is a statistically significantly greater improvement for post-2002 cohorts relative to pre-2002 cohorts, with a MD of 7.66 (95% CI 2.57 to 12.76, P<0.05), and likewise for the DAS-28 and fatigue, there was a statistically significantly greater improvement for post-2002 cohorts relative to pre-2002 cohorts, with a MD of 0.51

(95% CI 0.04 to 0.98, P<0.05) and 10.91 (95% CI 5.04 to 16.79) respectively. In contrast, whilst pain, SF-36 MCS and HAQ exhibit improvements by 12-months, the magnitude of these improvements were much smaller and did not reach statistical significance, with a MD of 3.30 (95% CI -2.67 to 9.28), 0.10 (95% CI -4.03 to 4.23) and 0.05 (95% CI -0.15 to 0.25) respectively.

Whilst pain, SF-36 MCS and the HAQ saw incremental improvements in the estimated mean differences by the ~~and~~ 36-month and 60-month time points, ~~the estimated mean differences~~these improvements were small and did not lead to any statistical differences by month 60. ~~indicated a lower score for the post-2002 cohorts for all outcomes measured, however only fatigue, SF-36 PCS and DAS indicated a statistically significant difference (P<0.05). By month 60, the SF-36 PCS indicated a statistically significantly lower score for post-2002 (P=0.003). In contrast, pain, fatigue, SF-36 MCS and HAQ all indicated statistically non-significant declines for post-2002 (P>0.1).~~The SF-36 PCS remained stable over the 36 and 60-month period, with a statistically significant MD of 7.77 (95% CI 2.68 to 12.87) at month 60, whilst the post-2002 cohort continued to see greater improvements over time, with statistically significantly greater improvements by month 60 of 0.92 (95% CI 0.38 to 1.45). Only fatigue saw decreases in improvements over the 36 and 60-month period for the post-2002 cohorts, with a statistically non-significant MD of 5.74 (95% CI -1.70 to 13.18) by month 60.

Figure 2 – Forest plot of the estimated Mean Difference (MD) for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Points that fall to the left of the zero-line indicate better outcomes in the pre-2002 cohorts, whilst those that fall to the right of the zero-line indicate better outcomes for the post-2002 cohorts. 95% Confidence Intervals are indicated by the horizontal bars on the graph and in the brackets of the text. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

This time dependent trend for pain, fatigue, SF-36, HAQ and DAS28 for both pre-2002 and post-2002 cohorts are given in Figure 3. It demonstrates the increased initial response in the first 12 months for pain, HAQ and DAS28 for both the pre and post-2002 cohorts, however the decrease in pain and HAQ is not as great as the decline in DAS28. In contrast, whilst the post-2002 cohorts saw improvements in fatigue, SF-36 PCS and SF-36 MCS in the first 12-months, the pre-2002 cohorts indicated a more stable progression over the full 60-months. By month 60, only the SF-36 PCS and DAS28 scores indicated a significant difference between the pre and post-2002 cohorts, with post-2002 cohorts indicating more favourable outcomes (P<0.05). However, there was no statistically significant difference between pre and post-2002 cohorts over the full 60-months for pain, SF-36 MCS and HAQ.

Sensitivity analysis

Dichotomising recruitment year into pre- and post-2002 allowed for data to be pooled into larger groups, as further stratification would have led to issues with data sparsity of outcomes over the follow-up period. However, to ensure that these groups reflected a broader linear association with recruitment year, a sensitivity analysis was conducted

looking at recruitment year as a continuous outcome, rather than a binary outcome. The analysis indicated a linear association with recruitment year, with each outcome. In corroboration with the main analysis, the main of effect of recruitment year was statistically significantly associated with DAS-28, and whilst the other outcomes indicated reductions as recruitment year increased, these were smaller effects and did not reach statistical significance. A detailed report of this analysis is provided in supplementary material.

Additional analysis investigated the progression of the sub-components of the DAS28; the Swollen Joint Count (SJC), Tender Joint Count (TJC), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), in a sub-group of cohorts reporting this data. Of the 37 cohorts with DAS28 data, 25 had data on SJC, 23 on TJC, 22 on CRP and 18 on ESR. Whilst SJCs, TJCs and CRP showed greater declines in post-2002 compared to pre-2002 cohorts, the estimates over the follow-up periods were inconclusive due to low levels of data over the follow-up. Details of this sub-analysis are presented in the supplementary material.

Figure 3 –Estimated marginal means for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Circle points with solid black lines indicate the estimated means for the pre-2002 cohorts, whilst triangle points with a dashed black line indicate the estimated means for the post-2002 cohorts. 95% Confidence Intervals are indicated by the grey shaded areas. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

Standardised Mean Differences (SMD)

Whilst the MD allows for differences to be examined relative to the scale in which the outcome was measured, to directly compare the magnitude of the effects of each outcome relative to each other, the MD needs to be standardised. The Standardised Mean Differences (SMD) for the DAS28 at month-60 comparing post-2002 to pre-2002 cohorts was 0.86 (95% CI 0.34 to 1.37), whilst for the SF-36 PCS it was 0.76 (95% CI 0.25 to 1.27), indicating that both demonstrated large, statistically significantly lower score for post-2002 cohorts (P<0.001).

In contrast, the SMD at month-60 comparing post-2002 to pre-2002 cohorts for pain (0.24 (95% CI -0.25 to 0.74)), fatigue (0.38 (95% CI -0.11-to 0.88)) and HAQ scores (0.34 (95% CI -0.15-to 0.84)) all indicated small to moderate effect sizes and failed to reach statistical significance in favour of post-2002 cohorts. Only the SF-36 MCS indicated improvements in favour of pre-2002 cohorts, however the effect was very small and statistically non-significant (-0.08 (95% CI -0.58 to 0.41)).

Discussion

This review is one of the first to examine the longitudinal trends of important, and well reported patient reported outcomes in inflammatory arthritis using meta-analysis. Using data from 46~~29~~ early RA cohorts, with a combined total of ~~10,132~~18,046 patients, the longitudinal meta-analysis indicated that whilst patients in more recent cohorts have large, statistically significant improvements in levels of disease activity and physical well-being

over the first 60-months, pain, fatigue, physical functioning and mental well-being indicate only small, statistically non-significant improvements.

The reduction in disease activity levels is in general agreement with a previous meta-analyses that looked at longitudinal rates of structural joint damage, and found that post-2002 cohorts had statistically significantly lower joint damage than those patients recruited pre-2002[23]. Given that both reviews rely on observational cohort data, the exact cause of the decline in disease activity, and indeed other objective measures of inflammation, cannot be determined directly. However, it is likely that the move towards T2T principles of earlier, more aggressive therapies to achieve low/remission based DAS scores, along with the increased use of bDMARD therapies, are the main drivers for these secular declines[11,23,69].

Despite large effects in the reduction of disease activity, these do not translate into similar improvements in patient reported pain, functional disability and mental well-being. These findings are similar to previous meta-analyses investigating data from randomised controlled trials (RCT) for both HAQ[70], and SF-36[71] outcomes. They found that patients treated with more aggressive therapies (e.g. combination, or bDMARDs) indicated improved function and well-being, however these were not statistically significant, nor did it reflect clinically meaningful changes. These findings add more weight to the hypothesis that psychological well-being, along with functional disability, may be mediated by factors not directly influenced by inflammatory processes[10,72].

The precise role of pro-inflammatory cytokines and their association with pain and mental health is currently unclear[73]. Animal model studies have provided evidence of a link between Interleukin-1 (IL-1)[74,75], IL-6[76] and TNF-alpha[77] on depressive behaviours in mice, and cross-sectional cohort studies have shown evidence of elevated pro-inflammatory cytokines in patients with depressive symptoms[78]. However, observational studies fail to identify significant associations (both statistically and clinically) between mental health symptoms and changes in proteomic markers, such as ESR[76]. Indeed, this study also found a disconnect between fatigue and disease activity over time, suggesting that non-inflammatory processes may be involved in fatigue symptoms, such as increased levels of pain[79]. As such it is hypothesised that increased inflammation is, in part, explaining elevated symptoms in mental well-being and disability, however non-inflammatory processes also need to be considered.

Emerging research is beginning to investigate the relationship between pain and mental health could be governed by the mesolimbic dopaminergic reward system[80]. Reduced levels of dopamine have been found in patients with fibromyalgia[81,82] and there is evidence that activity in the mesolimbic reward system, specifically the role of increased dopamine neurotransmission, are strongly linked to positive emotions[83,84]. Whilst the experience of pain itself may be contributing to the reduction of dopaminergic regulation, as evidence by reductions in patients with fibromyalgia and chronic back pain[85], the role of inflammatory makers on this system may also explain the decreased levels in RA specifically[86].

The extent to which inflammation can explain interindividual variability in mental health outcomes in all patients, or whether sub-groups of patients exist whereby inflammation plays either a lesser or more dominant role in pain experience and mental wellbeing is not

yet clear. Distinct sub-groups of patients that progress differently over time has been evidenced in both functional disability[22] and disease activity measures[87], which have been demonstrated even amongst early RA patients under T2T regimes. Research by Altawil et al. has demonstrated how pain remains at high levels in a sub-group of patients, despite achieving EULAR remission, suggesting that other mechanisms of pain beyond inflammation are responsible[88]. Understanding factors associated with these different RA sub-groups, and how pain, functional disability and well-being progress over the course of the disease, would be instrumental in tailoring treatment, both pharmacological and non-pharmacological, at the early stages.

The major strengths of the study lie in its large data. The meta-analysis presented in this paper is the first, to our best knowledge, to aggregate data on numerous early RA cohorts on key clinical and patient reported outcome measures over time, with very large numbers of patients. The statistical methods used are novel in the field and allow an accurate estimation of each outcome over time, and across different periods. However, the study is not without its limitations. Large heterogeneity between studies due to the observational nature of the cohort studies included, as well as the breadth of different countries involved, makes drawing definitive conclusions on the pooled effect estimates challenging. The review includes a broad range of countries representing different GDP per capita, which has been shown in previous research to be correlated with disease activity[89]. There is some evidence to suggest socio-economic status plays an important role in the progression of functional disability and reduced quality of life[90]. However, socio-economic status is rarely reported in cohorts, making it difficult to analyse its impact in a meta-analytical setting. Additionally, e~~E~~very effort was made to minimise the potential bias by restricting cohorts to only early RA, as well as adopting a random-effects meta-analysis that assumes there are a range of different effects being estimated that follow an approximately normal distribution. It is reasonable to assume that country level differences in treatment prescription exist, however it is likely that most countries will have followed a similar protocol of T2T, employing broadly similar step-up treatment decisions to achieve remission/low disease. Data sparsity between the cohort periods over the follow-up for outcomes, such as fatigue, are likely to explain some of the statistically non-significant findings. Larger data samples at the later follow-up times would help narrow the intervals and provide more precision around the true effect. ~~Publication~~ Publication b~~b~~ias is possible, but unlikely since cohort data was sought based on identification through publications that were not dependent on positive findings.

In conclusion, this longitudinal meta-analysis provides large scale data highlighting that the introduction of more aggressive, T2T based therapies coincided with ~~marked~~ improvements in disease activity and physical function over the last few decades during the first 60-months of the disease. However, these large-scale improvements in disease activity did not translate into equally large improvements in patient reported outcomes, namely pain, functional disability and mental well-being. Whilst inflammation remains a key target, t~~T~~hese findings provide clear support for rheumatologists to go beyond the consideration of just the DAS in their T2T approach. Non-pharmacological treatments, for managing pain, improving functional disability and improving psychological well-being are available and need to be more widely adopted in routine care.

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Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal meta-analysis.

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Abstract

Objectives: To conduct a systematic review and longitudinal meta-analysis of early rheumatoid arthritis (RA) cohorts with long-term data on pain, fatigue or mental well-being.

Methods: Searches using PUBMED, EMBASE and PyscInfo were performed to identify all early RA cohorts with longitudinal measures of pain, fatigue or mental well-being, along with clinical measures. Using longitudinal meta-analyses, the progression of each outcome over the first 60-months was estimated. Cohorts were stratified based on the median recruitment year to investigate secular trends in disease progression.

Results: Of 7,319 papers identified, 75 met the inclusion criteria and 4629 ~~25~~ 41 publications provided sufficient data on 180,046~~132~~ patients for meta-analysis. The Disease Activity Scores (DAS28) and the Short-Form 36 (SF-36) Physical Component Score (PCS) indicated that post-2002 cohorts had statistically significant improvements over the first 60-months compared to pre-2002 cohorts, with standardised mean differences (SMD) of 0.86 (95% Confidence Intervals 0.34 to 1.37) and 0.76 (95% CI 0.25 to 1.27) respectively at month-60. However, post-2002 cohorts indicated statistically non-significant improvements in pain, fatigue, functional disability and SF-36 Mental Component Score (MCS) compared to pre~~ost~~-2002 cohorts, with SMD of 0.24 (95% CI -0.25 to 0.74), 0.38 (95% CI -0.11 to 0.88), 0.34 (95% CI -0.15-0.84) and -0.08 (95% CI -0.41 to 0.58) at month-60 respectively.

Conclusions: Recent cohorts indicate improved levels of disease activity and physical quality of life, however this has not translated into similar improvements in levels of pain, fatigue and functional disability by 60-months.

Keywords

Rheumatoid Arthritis, Systematic Review, Meta-Analysis, Cohort Studies

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Introduction

Rheumatoid arthritis (RA) is a chronic auto-immune disease that causes inflammation and pain in joints. It is estimated to affect approximately 1% of the UK adult population[1]. Inadequately treated, it can lead to long-term physical damage, namely in the form of bone erosions and joint space narrowing, as well as reduced quality of life. The adoption of biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) in the most severe cases[2], as well as the introduction of the Treat-2-Target (T2T) approach to disease management in the early 2000's[3], which employs the use of early, more aggressive conventional DMARD (csDMARD) therapies[4] have had a large impact on reducing inflammation and radiographic joint damage in recent years[5–7]. Despite this, there is little indication that this has translated into equivalently large, clinically-meaningful improvements in pain, fatigue and health related quality of life (HRQoL)[8–11]. This is of particular importance in RA populations, as there is evidence that patients with RA have higher prevalence of psychological distress, such as depression and anxiety[12–15] compared to the general population and that those patients with persistent depression have been evidenced to respond less well to bDMARD therapies[16]. Also, patients with RA with worse quality of life outcomes are associated with higher Health Care Resource Utilisation (HCRU)[17].

There is a sparsity of systematic reviews, including meta-analysis of quantitative data, investigating HRQoL outcomes. Matcham et al.[14] is one of the few published systematic reviews to investigate HRQoL in observational trials of RA populations, and demonstrated that HRQoL was lower in patients with RA when compared to other chronic conditions, such as Type 2 diabetes and congestive heart failure. However, much of the data presented were cross-sectional in nature, and as such does not document how HRQoL progresses over time, or indeed how modern approaches to treatment and management may have impacted on disease progression over different periods. To our knowledge, only one other review explored HRQoL in older patients with RA (≥75 years) and found that pain, increased age and increased functional disability all contributed to worse HRQoL[18].

The aim of this systematic review was to examine symptom severity and HRQoL at different points during the RA disease course and assess whether there have been changes in symptom levels and HRQoL over the last 30 years, in light of the substantial changes in treatment strategies over the last few decades.

Methods

Identifying publications

A systematic search of 3 databases, namely PubMed, EMBASE and PsycInfo, was conducted between 1975-2017. The search strategy used key words and MeSH terms on the title/abstract and full text as appropriate (See supplementary material for search terms used). Additional lateral search techniques included checking reference lists, performing key word searches in Google Scholar and using the 'cited by' option in PubMed. The review included all studies of adult patients (>18 years old) with early RA, where baseline assessment was <3 years from symptom onset. Diagnosis was confirmed by either the 1987 or 2010 American College of Rheumatology (ACR) criteria. As a systematic review of non-randomised observational cohorts, there was no intervention or comparator group of interest in this review.

Outcome(s)

The outcomes of interest were pain, fatigue and mental wellbeing. Pain and fatigue are typically measured using a Visual Analogue Scale (VAS), however other measures were eligible to be included. Mental health included any measures of quality of life, such as the EuroQol 5-Dimensions (EQ-5D) or the Short-Form 36 (SF-36). Other measures relating to depression and anxiety were also recorded if reported (e.g. Hospital Anxiety and Depression Scores (HADS) and the Beck Depression Inventory (BDI)).

Secondary outcome measures included clinical measures of disease, namely the Disease Activity Score (DAS) and measures of functional disability, namely the Health Assessment Questionnaire (HAQ).

Inclusion/exclusion criteria

Inclusion criteria to select publications comprised of: (1) included a measure of self-reported pain, fatigue or mental well-being, (2) patients had a diagnosis of rheumatoid arthritis, (3) baseline assessments occurred no later than 3-years from symptom onset, (4) prospective cohort study design, (5) had repeated measures (at least two time points), (6) included human participants, and (7) publications written in English.

Publication screening

One reviewer (RB) screened titles/abstracts identified in searches, using the selection criteria to identify potentially relevant papers. A second reviewer (LC) independently screened the title/abstract of 25% of all publications identified against agreed inclusion criteria. Agreement at the title/abstract stage was achieved in 92% of papers, with disagreements resolved through discussion (e.g. longitudinal data was only available for a subset of patients with established disease, not early disease). Both reviewers (LC & RB) then screened all full texts to establish the final set of studies to include in the review. Of the 1,736 full texts screened, agreement was achieved for 99.7% of papers.

Data extraction

Three reviewers (LC, RB and PM) extracted data using a pre-designed form, piloted to ensure all data necessary were captured. It included: cohort name, country of study population, pain/fatigue/mental well-being mean scores and Standard Deviation (SD), along with the outcome measure(s) used, number of patients included, years of recruitment, length of follow-up, proportion of females in the cohort, mean age of patients in the cohort, functional disability mean scores and SD at each recorded follow-up, Disease Activity Score mean and SD at each recorded follow-up (where this was recorded using the DAS44 method, a conversion formula was applied to convert it to DAS28[19]), proportion of patients in the cohort on DMARDS at baseline, proportion of patients in the cohort who were Rheumatoid Factor (RF) positive at baseline and number of patients at each follow-up. In cases where the raw data were not given in the published paper the author(s) were individually contacted to provide this data (n=39).

Quality Assessment

Studies were rated using the Downs and Blacks instrument for non-randomised studies of health care interventions[20]. Since the studies did not examine clinical effectiveness, checklist items related to comparative groups (e.g. randomisation and blinding procedures) were omitted. One reviewer (LC) scored all studies using the amended checklist and another reviewer (PM) independently scored 50% of studies drawn at random. Discrepancies between reviewers were discussed and consensus achieved.

Statistical Analysis

The systematic review extracted data at baseline, and all recorded follow-ups, for a range of different outcomes measuring disease activity, functional disability, pain, fatigue and mental well-being. Whilst traditional meta-analytical methods are used for cross-sectional data, a weighted mixed-effects model was needed to account for the aggregate level summary data of each time point over time. Multivariate meta-analyses were conducted using mixed-effects linear regression models, with a random intercept estimated to account for repeated observations within studies and a random slope for time allowing the rate of progression to vary within studies over time[21]. Since the data are aggregate level for each included cohort at each time point, they were inverse variance weighted using the study level standard error at each recorded time point. Much like a meta-analysis, this allows studies with greater sample sizes to given greater weight in the estimation of the pooled effect estimate. Full Information Maximum Likelihood (FIML) allowed for estimation of time-specific means of every cohort in the event that the data are missing. This is similar to meta-regression techniques, which assess the effect of covariates on the study level estimates. As such, the figures provided represent the estimated pooled mean for that outcome at each follow-up time-point.

Since the cohorts included will be prospective inception cohorts of patients with early RA, it was expected that the progression of all outcomes will be non-linear over time. Previous research has shown how outcomes such as functional disability follow a 'J-Shaped' trajectory in the first years of disease[22], whereby patients initially improve rapidly in the first 12-months following treatment initiation, but then worsen in the subsequent years as disease duration increases. In order to account for this non-linearity, piecewise linear splines were used with a change point at 12-months. This allows for two separate slopes to be estimated by the model, one from baseline to 12-months, and one from 12-months to 60-months. In order to quantify the data from the model, the meta-analysis will be based on the estimated pooled effect for each outcome at four pre-specified time points; baseline, 12-months, 36-months and 60-months.

For each cohort, mid-point between the first and last year of recruitment was used to place the cohorts in chronological order from earliest to latest. Cohorts were then split according to whether the recruitment was pre or post 2002. This has been used in other reviews due to its reflection of the move towards more T2T principles, and also reflects the general median year in early RA cohorts in previous reviews[23]. The dichotomised variable was entered into the mixed effect model, along with an interaction effect with follow-up time. The mean difference between pre and post -2002 cohorts will be used as the main effect estimate. These will be estimated at baseline, 12, 36 and 60-months follow-up for the Pain Visual Analogue Scale (VAS), Fatigue VAS, SF-36 PCS, SF-36 MCS, the HAQ and the DAS

outcomes. Scores <0 indicate more favourable scores for the pre-2002 cohorts, whilst scores >0 indicate more favourable scores for the post-2002 cohort. This will be expressed as both a mean difference, which highlights the change in score relative to the scale in which it was measured, as well as a Standardised Mean Difference (SMD), which allows for direct comparisons between measures with different scales. All analyse were conducted using Stata (ver15) using the 'mixed' command for mixed effects analysis.

Results

A total of 7,319 articles were identified from the 3 databases following the removal of 2,363 duplicates, as shown in Figure 1. Following title and abstract screening, 1,736 full texts were screened for eligibility. In total, 41 articles[11,22,32–41,24,42–51,25,52–61,26,62,27–31] describing data from 46 cohorts where identified, contributing a combined total of 18,046 patients. The median year of recruitment for all cohorts ranged from 1983-2014, with a median year of 2002. Cohorts recruited patients from twenty different countries (Australia[41], Austria[62], Brazil[48], Canada[24,49,53,58], Denmark[28], France[29,32,50], Germany[42,46], Iceland[54], Italy[27,31,56], Japan[35], Latin American[57], The Netherlands[25,34,36,40,59], Norway[33], Scotland[47], South Africa[51], Spain[37,61], Sweden[11,38,60], UK[22,26,39,55], USA[30,43,45,52] and Mexico[44]). The UK had the highest number of cohorts at eight (17%), followed by five (11%) from the Netherlands, and four (9%) from Canada, Sweden and the US. The characteristics of the cohorts, and the patients included in those cohorts are summarised in Table 1.

Table 1 – Summary table of cohort characteristics, and baseline summary statistics of the patients included in the cohorts.

Although contact was made with 39 authors for additional longitudinal data, only 9 responded. With respect to the data collected, 36 (78%) had measures of pain[11,22,33,35,37–40,42,44–46,24,47,49–52,54,56–59,26,61,62,27–32], 13 (28%) had measures of fatigue[26–28,39,44,46,50,52,56], nine (20%) had measures of SF-36[26,50,51,55,56,59,60], 37 (80%) had measures of the HAQ[11,22,34–41,43,44,24,45,47–52,55,56,59,25,61,62,26,28–30,32,33] and 37 (80%) had measures of DAS[11,22,33–40,42,44,24,45–47,49,50,52,53,55,56,59,26,61,62,27–32]. Alongside SF-36, other longitudinal measures of mental health were also collected, namely the Centre for Epidemiological Studies Depression Scale (CES-D)[49,53,58], The Arthritis Impact Measurement Scale (AIMS)[26] and the Hospital Anxiety and Depression Scale (HADS)[47,63], however the small numbers meant it was not possible to include them in the meta-analysis.

Figure 1 – Prisma Flow Diagram of journal screening process at each stage of the systematic review

Quality Assessment

A modified version of the Down's and Black Checklist was used to assess the quality of each study. Agreement between the two reviewers was high at 99%, and where there were differences, these were resolved through consultation.

Overall, all studies included in the meta-analysis were of high quality, with all studies clearly defining the hypothesis, characteristics of the patients, main findings, and estimates of variability (See supplementary material). The patients included were representative of the general population and there were no indications of 'data dredging'. However, less than

15% of the studies provided characteristics of their patients who were lost to follow-up, and only 20% of the studies appropriately accounted for this loss of follow-up in their analysis.

Whilst >80% of studies were suitably powered, described the principle confounders and appropriately accounted for the longitudinal nature of the study in their analysis, <50% of studies were found to have used appropriate statistical methods and adequately adjusted for all important confounding effects. This was largely due to the reliance on step-wise regression methods, which allow for variable selection but introduce bias in parameter estimates without regularisation[64].

Meta-Analysis

Mean Differences (MD)

The forest plots presented in Figure 2 represent the pooled (model estimated) Mean Differences (MD) between pre and post-2002 cohorts at baseline, 12, 36 and 60-months. For illustration, the sub-group pooled effect estimate for cohorts recruiting patients post-2002 for baseline Pain VAS was 52.48 (95% Confidence Intervals 48.92 to 56.05), whereas the sub-group pooled effect estimate for cohorts recruiting patients post-2002 was 48.32 (95% CI 44.51 to 52.13) (Please see Supplementary Material). This equates to a MD of -4.16 (95% CI -9.34 to 1.01), as shown in Figure 2 (allowing for rounding error).

In order to conceptualise the magnitude of the effects, the reported mean differences for each outcome were compared to changes that are deemed clinically important, often referred to as the Minimally Clinically Important Difference (MCID). Whilst thresholds vary, the MCID for pain VAS has been reported to be 11.9[65], whilst estimates for the fatigue VAS have ranged from 8.2 to 11.2 in RA populations[66]. Likewise, the MCID has been reported between 2.5 to 5.0 for the SF-36 PCS and MCS, however studies have demonstrated higher estimates of 7.1 for the SF-36 PCS[67]. As such, an estimate of 8-unit change has been illustrated in Figure 1 for the MCID for the pain, fatigue and SF-36 PCS and MCS. Likewise, a MCID of 0.20 was used for HAQ[65], and 1.00 for the DAS-28[68].

Investigation of the mean differences of all the outcomes between pre- and post-2002 studies indicate that, at baseline, pre-2002 cohorts had marginally lower levels of pain (-4.17; 95% CI -9.34 to 1.01), SF-36 MCS (-5.25; 95% CI -11.74 to 1.23) and HAQ (-0.11; 95% CI -0.27 to 0.06), whilst pre-2002 cohorts had higher levels of fatigue (3.43; 95% CI -1.32 to 8.17), SF-36 PCS (0.70; 95% CI -4.23 to 5.62) and DAS (0.18; 95% CI -0.16 to 0.51) at baseline. However, none of these differences reached statistical significance (See Figure 2).

By 12-months, all outcomes exhibit an improvement in scores. However, there is variation in the magnitude of this improvement in pre- and post-2002 cohorts for each outcome. With the SF-36 PCS there is a statistically significantly greater improvement for post-2002 cohorts relative to pre-2002 cohorts, with a MD of 7.66 (95% CI 2.57 to 12.76, $P<0.05$), and likewise for the DAS-28 and fatigue, there was a statistically significantly greater improvement for post-2002 cohorts relative to pre-2002 cohorts, with a MD of 0.51 (95% CI 0.04 to 0.98, $P<0.05$) and 10.91 (95% CI 5.04 to 16.79) respectively. In contrast, whilst pain, SF-36 MCS and HAQ exhibit improvements by 12-months, the magnitude of these improvements were much smaller and did not reach statistical significance, with a MD of 3.30 (95% CI -2.67 to 9.28), 0.10 (95% CI -4.03 to 4.23) and 0.05 (95% CI -0.15 to 0.25) respectively.

Whilst pain, SF-36 MCS and the HAQ saw incremental improvements in the estimated mean differences by the 36-month and 60-month time points, these improvements were small and did not lead to any statistical differences by month 60. The SF-36 PCS remained stable over the 36 and 60-month period, with a statistically significant MD of 7.77 (95% CI 2.68 to 12.87) at month 60, whilst the post-2002 cohort continued to see greater improvements over time, with statistically significantly greater improvements by month 60 of 0.92 (95% CI 0.38 to 1.45). Only fatigue saw decreases in improvements over the 36 and 60-month period for the post-2002 cohorts, with a statistically non-significant MD of 5.74 (95% CI -1.70 to 13.18) by month 60.

Figure 2 – Forest plot of the estimated Mean Difference (MD) for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Points that fall to the left of the zero-line indicate better outcomes in the pre-2002 cohorts, whilst those that fall to the right of the zero-line indicate better outcomes for the post-2002 cohorts. 95% Confidence Intervals are indicated by the horizontal bars on the graph and in the brackets of the text. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

This time dependent trend for pain, fatigue, SF-36, HAQ and DAS28 for both pre-2002 and post-2002 cohorts are given in Figure 3. It demonstrates the increased initial response in the first 12 months for pain, HAQ and DAS28 for both the pre and post-2002 cohorts, however the decrease in pain and HAQ is not as great as the decline in DAS28. In contrast, whilst the post-2002 cohorts saw improvements in fatigue, SF-36 PCS and SF-36 MCS in the first 12-months, the pre-2002 cohorts indicated a more stable progression over the full 60-months. By month 60, only the SF-36 PCS and DAS28 scores indicated a significant difference between the pre and post-2002 cohorts, with post-2002 cohorts indicating more favourable outcomes ($P<0.05$). However, there was no statistically significant difference between pre and post-2002 cohorts over the full 60-months for pain, SF-36 MCS and HAQ.

Sensitivity analysis

Dichotomising recruitment year into pre- and post-2002 allowed for data to be pooled into larger groups, as further stratification would have led to issues with data sparsity of outcomes over the follow-up period. However, to ensure that these groups reflected a broader linear association with recruitment year, a sensitivity analysis was conducted looking at recruitment year as a continuous outcome, rather than a binary outcome. The analysis indicated a linear association with recruitment year, with each outcome. In corroboration with the main analysis, the main of effect of recruitment year was statistically significantly associated with DAS-28, and whilst the other outcomes indicated reductions as recruitment year increased, these were smaller effects and did not reach statistical significance. A detailed report of this analysis is provided in supplementary material.

Additional analysis investigated the progression of the sub-components of the DAS28; the Swollen Joint Count (SJC), Tender Joint Count (TJC), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), in a sub-group of cohorts reporting this data. Of the

37 cohorts with DAS28 data, 25 had data on SJC, 23 on TJC, 22 on CRP and 18 on ESR. Whilst SJCs, TJCs and CRP showed greater declines in post-2002 compared to pre-2002 cohorts, the estimates over the follow-up periods were inconclusive due to low levels of data over the follow-up. Details of this sub-analysis are presented in the supplementary material.

Figure 3 –Estimated marginal means for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Circle points with solid black lines indicate the estimated means for the pre-2002 cohorts, whilst triangle points with a dashed black line indicate the estimated means for the post-2002 cohorts. 95% Confidence Intervals are indicated by the grey shaded areas. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

Standardised Mean Differences (SMD)

Whilst the MD allows for differences to be examined relative to the scale in which the outcome was measured, to directly compare the magnitude of the effects of each outcome relative to each other, the MD needs to be standardised. The Standardised Mean Differences (SMD) for the DAS28 at month-60 comparing post-2002 to pre-2002 cohorts was 0.86 (95% CI 0.34 to 1.37), whilst for the SF-36 PCS it was 0.76 (95% CI 0.25 to 1.27), indicating that both demonstrated large, statistically significantly lower score for post-2002 cohorts (P<0.001).

In contrast, the SMD at month-60 comparing post-2002 to pre-2002 cohorts for pain (0.24 (95% CI -0.25 to 0.74)), fatigue (0.38 (95% CI -0.11-to 0.88)) and HAQ scores (0.34 (95% CI -0.15-to 0.84)) all indicated small to moderate effect sizes and failed to reach statistical significance in favour of post-2002 cohorts. Only the SF-36 MCS indicated improvements in favour of pre-2002 cohorts, however the effect was very small and statistically non-significant (-0.08 (95% CI -0.58 to 0.41)).

Discussion

This review is one of the first to examine the longitudinal trends of important, and well reported patient reported outcomes in inflammatory arthritis using meta-analysis. Using data from 46 early RA cohorts, with a combined total of 18,046 patients, the longitudinal meta-analysis indicated that whilst patients in more recent cohorts have large, statistically significant improvements in levels of disease activity and physical well-being over the first 60-months, pain, fatigue, physical functioning and mental well-being indicate only small, statistically non-significant improvements.

The reduction in disease activity levels is in general agreement with a previous meta-analyses that looked at longitudinal rates of structural joint damage, and found that post-2002 cohorts had statistically significantly lower joint damage than those patients recruited pre-2002[23]. Given that both reviews rely on observational cohort data, the exact cause of the decline in disease activity, and indeed other objective measures of inflammation, cannot be determined directly. However, it is likely that the move towards T2T principles of earlier, more aggressive therapies to achieve low/remission based DAS scores, along with the increased use of bDMARD therapies, are the main drivers for these secular declines[11,23,69].

Despite large effects in the reduction of disease activity, these do not translate into similar improvements in patient reported pain, functional disability and mental well-being. These findings are similar to previous meta-analyses investigating data from randomised controlled trials (RCT) for both HAQ[70], and SF-36[71] outcomes. They found that patients treated with more aggressive therapies (e.g. combination, or bDMARDs) indicated improved function and well-being, however these were not statistically significant, nor did it reflect clinically meaningful changes. These findings add more weight to the hypothesis that psychological well-being, along with functional disability, may be mediated by factors not directly influenced by inflammatory processes[10,72].

The precise role of pro-inflammatory cytokines and their association with pain and mental health is currently unclear[73]. Animal model studies have provided evidence of a link between Interleukin-1 (IL-1)[74,75], IL-6[76] and TNF-alpha[77] on depressive behaviours in mice, and cross-sectional cohort studies have shown evidence of elevated pro-inflammatory cytokines in patients with depressive symptoms[78]. However, observational studies fail to identify significant associations (both statistically and clinically) between mental health symptoms and changes in proteomic markers, such as ESR[76]. Indeed, this study also found a disconnect between fatigue and disease activity over time, suggesting that non-inflammatory processes may be involved in fatigue symptoms, such as increased levels of pain[79]. As such it is hypothesised that increased inflammation is, in part, explaining elevated symptoms in mental well-being and disability, however non-inflammatory processes also need to be considered.

Emerging research is beginning to investigate the relationship between pain and mental health could be governed by the mesolimbic dopaminergic reward system[80]. Reduced levels of dopamine have been found in patients with fibromyalgia[81,82] and there is evidence that activity in the mesolimbic reward system, specifically the role of increased dopamine neurotransmission, are strongly linked to positive emotions[83,84]. Whilst the experience of pain itself may be contributing to the reduction of dopaminergic regulation, as evidence by reductions in patients with fibromyalgia and chronic back pain[85], the role of inflammatory makers on this system may also explain the decreased levels in RA specifically[86].

The extent to which inflammation can explain interindividual variability in mental health outcomes in all patients, or whether sub-groups of patients exist whereby inflammation plays either a lesser or more dominant role in pain experience and mental wellbeing is not yet clear. Distinct sub-groups of patients that progress differently over time has been evidenced in both functional disability[22] and disease activity measures[87], which have been demonstrated even amongst early RA patients under T2T regimes. Research by Altawil et al. has demonstrated how pain remains at high levels in a sub-group of patients, despite achieving EULAR remission, suggesting that other mechanisms of pain beyond inflammation are responsible[88]. Understanding factors associated with these different RA sub-groups, and how pain, functional disability and well-being progress over the course of the disease, would be instrumental in tailoring treatment, both pharmacological and non-pharmacological, at the early stages.

The major strengths of the study lie in its large data. The meta-analysis presented in this paper is the first, to our best knowledge, to aggregate data on numerous early RA cohorts on key clinical and patient reported outcome measures over time, with very large numbers of patients. The statistical methods used are novel in the field and allow an accurate estimation of each outcome over time, and across different periods. However, the study is not without its limitations. Large heterogeneity between studies due to the observational nature of the cohort studies included, as well as the breadth of different countries involved, makes drawing definitive conclusions on the pooled effect estimates challenging. The review includes a broad range of countries representing different GDP per capita, which has been shown in previous research to be correlated with disease activity[89]. There is some evidence to suggest socio-economic status plays an important role in the progression of functional disability and reduced quality of life[90]. However, socio-economic status is rarely reported in cohorts, making it difficult to analyse its impact in a meta-analytical setting. Additionally, every effort was made to minimise the potential bias by restricting cohorts to only early RA, as well as adopting a random-effects meta-analysis that assumes there are a range of different effects being estimated that follow an approximately normal distribution. It is reasonable to assume that country level differences in treatment prescription exist, however it is likely that most countries will have followed a similar protocol of T2T, employing broadly similar step-up treatment decisions to achieve remission/low disease. Data sparsity between the cohort periods over the follow-up for outcomes, such as fatigue, are likely to explain some of the statistically non-significant findings. Larger data samples at the later follow-up times would help narrow the intervals and provide more precision around the true effect. Publication bias is possible, but unlikely since cohort data was sought based on identification through publications that were not dependent on positive findings.

In conclusion, this longitudinal meta-analysis provides large scale data highlighting that the introduction of more aggressive, T2T based therapies coincided with improvements in disease activity and physical function over the last few decades during the first 60-months of the disease. However, these large-scale improvements in disease activity did not translate into equally large improvements in patient reported outcomes, namely pain, functional disability and mental well-being. Whilst inflammation remains a key target, these findings provide clear support for rheumatologists to go beyond the consideration of just the DAS in their T2T approach. Non-pharmacological treatments, for managing pain, improving functional disability and improving psychological well-being are available and need to be more widely adopted in routine care.

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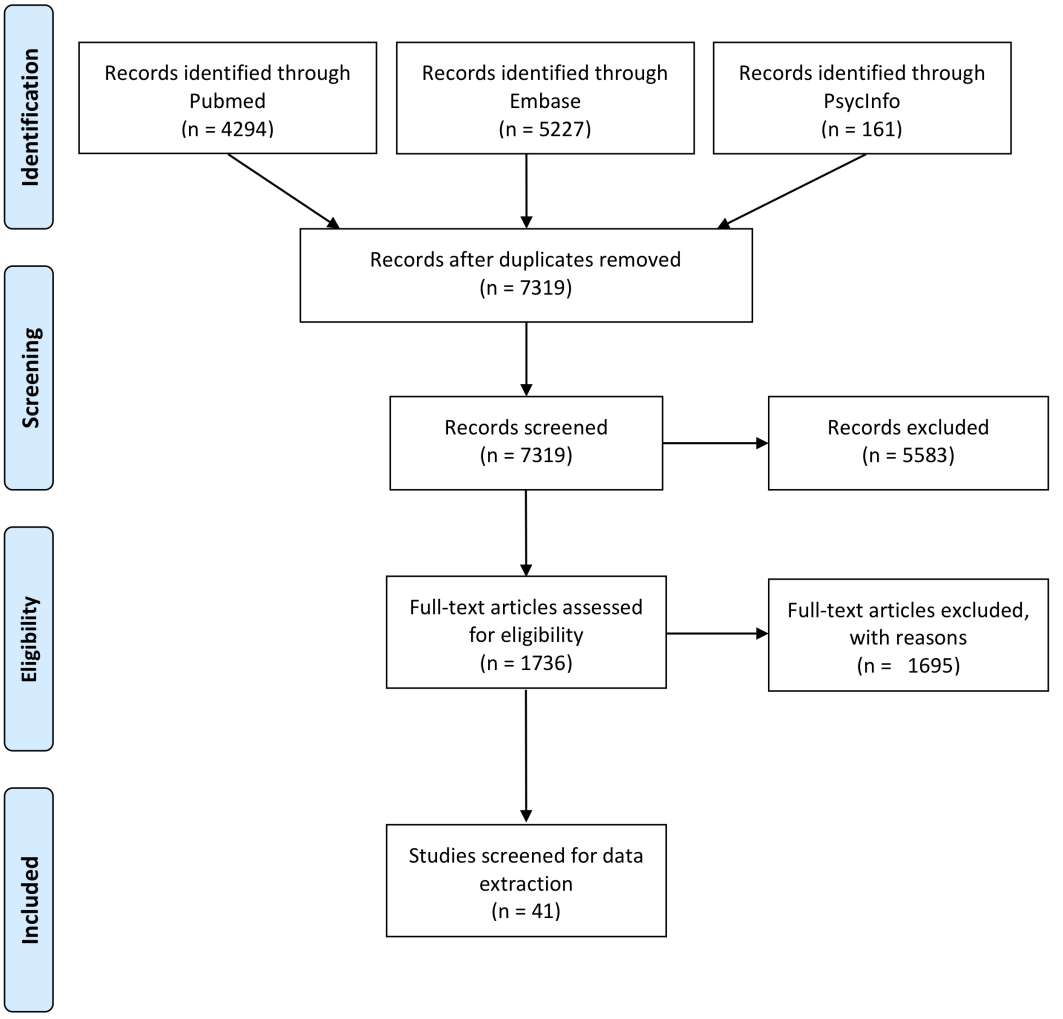
PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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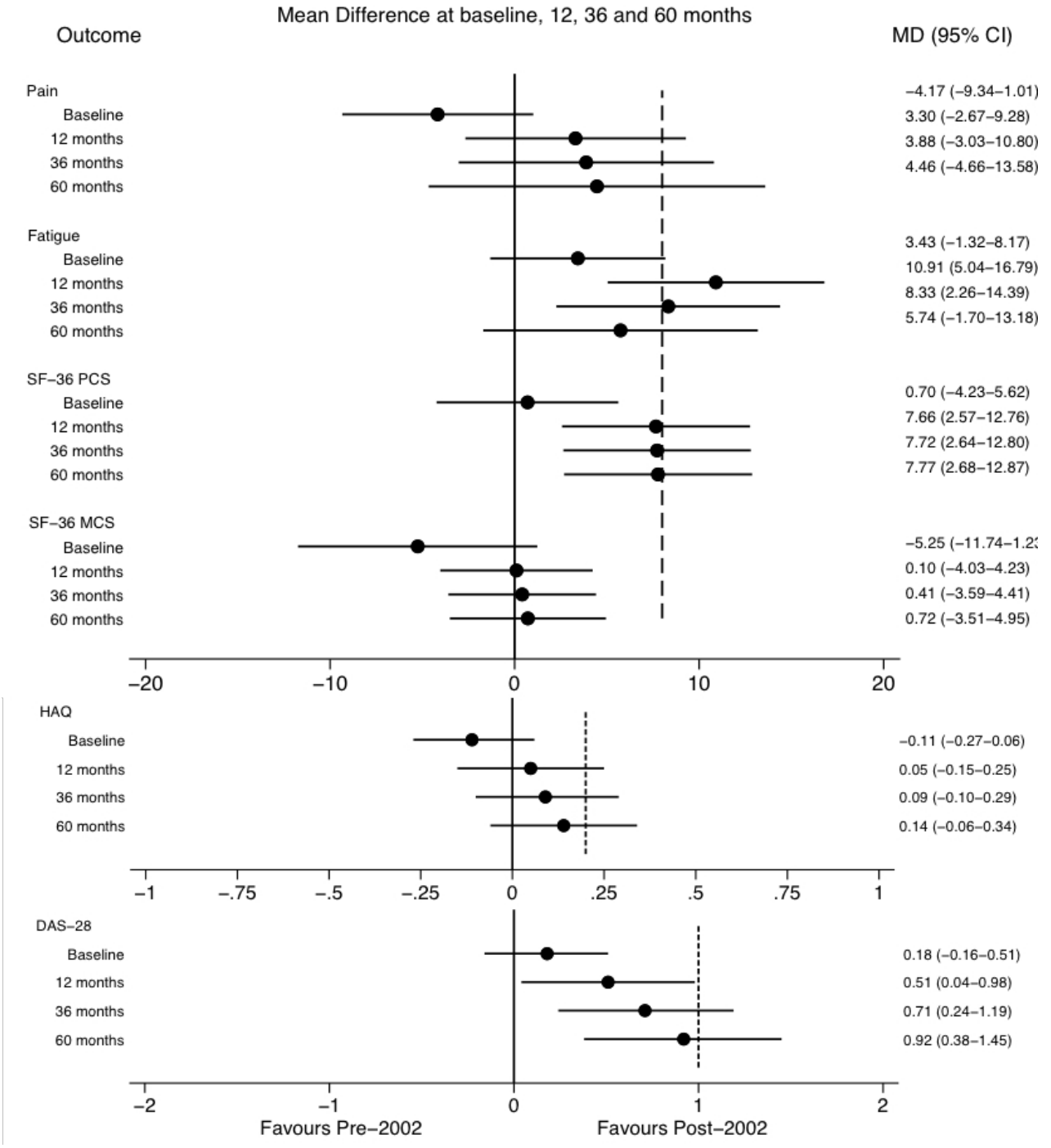
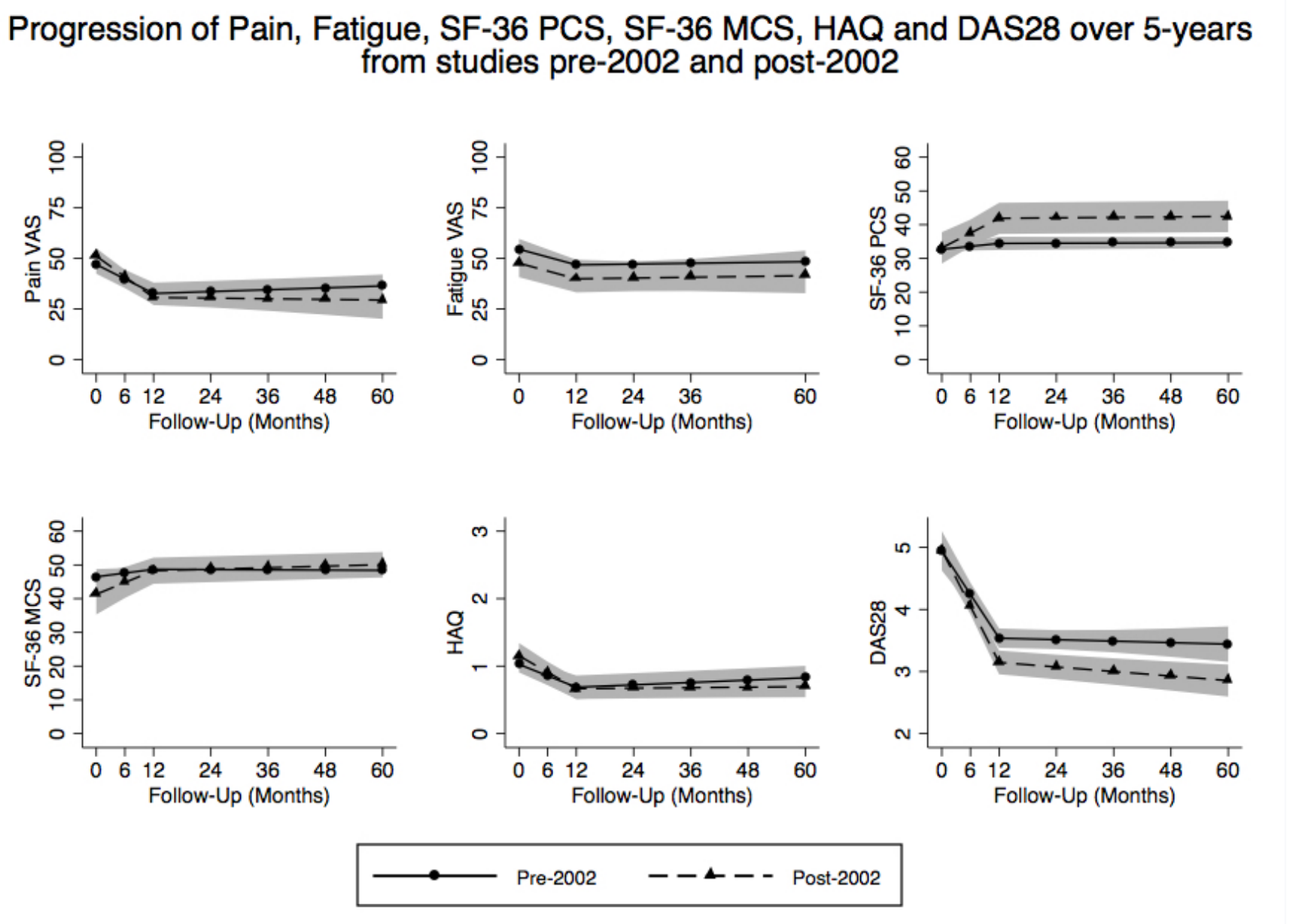

Mean Difference at baseline, 12, 36 and 60 months
Outcome
MD (95% CI)
Pain
Baseline
12 months
36 months
60 months
−4.17 (−9.34−1.01)
3.30 (−2.67−9.28)
3.88 (−3.03−10.80)
4.46 (−4.66−13.58)
Fatigue
Baseline
12 months
36 months
60 months
3.43 (−1.32−8.17)
10.91 (5.04−16.79)
8.33 (2.26−14.39)
5.74 (−1.70−13.18)
SF−36 PCS
Baseline
12 months
36 months
60 months
0.70 (−4.23−5.62)
7.66 (2.57−12.76)
7.72 (2.64−12.80)
7.77 (2.68−12.87)
SF−36 MCS
Baseline
12 months
36 months
60 months
−5.25 (−11.74−1.23
0.10 (−4.03−4.23)
0.41 (−3.59−4.41)
0.72 (−3.51−4.95)
−20
−10
0
10
20
HAQ
Baseline
12 months
36 months
60 months
−0.11 (−0.27−0.06)
0.05 (−0.15−0.25)
0.09 (−0.10−0.29)
0.14 (−0.06−0.34)
−1
−.75
−.5
−.25
0
.25
.5
.75
1
DAS−28
Baseline
12 months
36 months
60 months
0.18 (−0.16−0.51)
0.51 (0.04−0.98)
0.71 (0.24−1.19)
0.92 (0.38−1.45)
−2
−1
0
1
2
Favours Pre−2002
Favours Post−2002


Progression of Pain, Fatigue, SF-36 PCS, SF-36 MCS, HAQ and DAS28 over 5-years from studies pre-2002 and post-2002
Pain VAS
0 25 50 75 100
0 6 12 24 36 48 60
Follow-Up (Months)
Fatigue VAS
0 25 50 75 100
0 12 24 36 60
Follow-Up (Months)
SF-36 PCS
0 10 20 30 40 50 60
0 6 12 24 36 48 60
Follow-Up (Months)
SF-36 MCS
0 10 20 30 40 50 60
0 6 12 24 36 48 60
Follow-Up (Months)
HAQ
0 1 2 3
0 6 12 24 36 48 60
Follow-Up (Months)
DAS28
2 3 4 5
0 6 12 24 36 48 60
Follow-Up (Months)
Pre-2002
Post-2002

Author	Year Published	Cohort	Country	Year Recruited		Followup (Months)	N	Baseline Pain (Mean (SD))		Baseline Fatigue (Mean (SD))		Baseline SF36 PCS (Mean (SD))		Baseline SF36 MCS (Mean (SD))		Baseline HAQ (Mean (SD))		Baseline DAS (Mean (SD))		Age	Female (%)	RF + (%)
Ahlstrand et al.	2015	TIRA-1	Sweden	1996	1998	36	276	48.10	(25)							0.90	(0.6)	5.20	(1.2)	56	69	
Ahlstrand et al.	2015	TIRA-2	Sweden	2006	2009	36	373	52.60	(24)							1.00	(0.6)	5.10	(1.3)	59	67	
Ajeganova et al.	2016	Leiden	Netherlands	1993	2011	120	886									1.00	(0.87)			57	67	59
Amjadi et al.	2009	Mexico/US cohort	USA/Mexico	1993	2009	12	277	58.90	(28)	52.60	(24.3)					1.20	(0.7)	6.00	(1.1)	51	77	
Barnabe et al.	2015	CATCH	Canada	2007	2014	24	1586	5.50	(2.9)							1.03	(0.71)	5.06	(1.45)	54	73	66
Callhoff et al.	2015	CAPEA cohort	Germany	2010	2013	24	512	5.42	(2.6)	3.90	(2.86)							4.40	(1.4)	47	68	57
Cantini et al.	2012	Prato Cohort RA	Italy	2008	2010	36	55	69.00	(11)	62.00	(14.9)							5.48	(0.34)	50	40	89
Che et al.	2014	ESPOIR Cohort	France	2002	2005	60	664	39.60	(28)	48.90	(27.4)	37.90	(8.4)	39.30	(10.8)	1.03	(0.69)	5.30	(1.2)	49	77	46
Christensen et al.	2016	Copenhagen Cohort	Denmark	2013	2014	4	102	49.94	(24)	56.28	(26.9)					1.05	(0.65)	4.48	(1.1)	55	75	64
Combe et al.	2003	French Cohorts	France	1993	1994	60	140	57.50	(22)							1.30	(0.7)	4.10	(0.8)	51	73	81
Craig et al.	2010	CLEAR	USA	2000	2010	36	266	6.10	(2.9)							1.59	(0.92)	3.90	(1.5)	51	81	69
Da Mota et al.	2012	Brazil Cohort	Brazil	2012	2012	36	40									1.89	(0.78)			45	90	
Dale et al.	2016	SERA	Scotland	2011	2015	24	1073	51.96	(28)							1.17	(0.79)	4.74	(1.34)	58	65	72
Di Franco et al.	2015	Rome Cohort	Italy	2010	2012	12	37	63.00	(24)									5.18	(1)	47	84	83
Dobkin et al.	2013	CHUS Cohort	Canada	2006	2011	12	211	48.90	(27)							0.79	(0.61)	4.80	(1.4)	59	63	33
Flipon et al.	2009	VeRA	France	1998	2001	0	180	42.90	(26)							1.00	(0.72)	3.22	(1.3)	56	71	
Garcia et al.	2009	PROAR	Spain	2001	2005	60	171	55.21	(24)							1.40	(0.71)	5.80	(1.19)	54	70	52
Gwinnutt et al.	2017	NOAR-Cohort 1	UK	1990	1994	120	608									1.09	(0.737)	4.69	(1.19)	55	66	52
Gwinnutt et al.	2017	NOAR-Cohort 2	UK	1995	1999	84	453									1.13	(0.761)	4.48	(1.22)	57	69	59
Gwinnutt et al.	2017	NOAR-Cohort 3	UK	2000	2004	120	340	45.38	(26)	49.31	(27.2)	31.71	(9.89)	45.94	(11.9)	1.23	(0.765)	4.25	(1.12)	58	69	69
Gwinnutt et al.	2017	NOAR-Cohort 4	UK	2005	2008	120	304	46.84	(26)	50.78	(28.5)					1.18	(0.702)	4.42	(1.18)	55	69	74
Haugeberg et al.	2015	Norway Cohort	Norway	1999	2001	120	94	44.20	(25)							0.69	(0.51)	5.20	(1.1)	50	62	68
Hodkinson et al.	2012	GREAT Registry	South Africa	2005	2008	12	171	66.10	(25)			34.20	(16.9)	44.90	(18.5)	1.67	(0.79)			47	82	85
Jansen et al.	2000	Amsterdam Cohort	Netherlands	1995	1996	12	133									1.10	(0.8)	5.40	(1.2)	64	68	50
Jawaheer et al.	2010	West US & Mexico Cohort	USA	1993	2002	24	292	60.40	(27)	52.00	(24.6)					1.20	(0.7)	5.10	(1.1)	50	75	72
Kaneko et al.	2014	SAKURA Cohort	Japan	2007	2009	12	75	43.90	(29)							0.76	(0.713)	4.52	(1.15)	61	86	79
Kievit et al.	2006	UMCN/SMK	Netherlands	1985	2004	36	908									0.77	(0.6)	5.20	(1.3)	54	66	77
Leblanc-Trudeau et al.	2015	EUPA	Canada	1998	2013	42	275											4.80	(1.9)	60	63	36
Machold et al.	2007	AEAA	Austria	1996	2001	36	55	48.60	(22)							0.91	(0.89)	5.60	(1)	52	76	44

Manfredsdottir et al.	2006	Reykjavik Cohort	Iceland	1997	2000	24	100	6.30	(2.5)											53	57	47
McWilliams et al.	2013	ERAN	UK	2002	2011	60	997					29.12	(12.1)	47.30	(11.7)	1.08	(0.76)	4.68	(1.56)	57	68	53
Norton et al.	2013	ERAS	UK	1986	2001	120	1465	43.97	(26)							1.15	(0.769)	4.77	(1.26)	55	66	73
Paulus et al.	2000	US Western Consortium Cohort	USA	1993	1996	24	180	60.10	(27)							1.22	(0.73)	4.92	(1.14)	52	78	
Picchianti-Diamanti et al.	2010	Rome RA Cohort	Italy	2005	2006	24	20	58.50	(24)	77.70	(11.8)	25.60	(3.9)	29.50	(9)	1.16	(0.6)	4.90	(1.1)	53	75	
Ramagli et al.	2015	REPANARC Cohort	Latin America	2010	2013	24	173	6.00	(2.7)											42	84	47
Sanmarti et al.	2003	Barcalona Cohort	Spain	1998	2000	12	60	51.20	(22)							1.00	(0.5)	5.80	(0.8)	52	78	78
Schieir et al.	2009	McEar	Canada	2004	2007	6	320	8.00	(8.6)											57	69	
Steunebrink et al.	2016	DREAM Registry	Netherlands	2012	2015	12	91	58.40	(22)			37.30	(9.2)	44.80	(11.8)	0.90	(0.7)	4.90	(1.2)	59	60	58
Svensson et al.	2016	BARFOT	Sweden	1993	1999	96	640	45.00	(24)							1.00	(0.6)	5.10	(1.2)	54	66	60
Twigg et al.	2017	IACON	UK	2010	2014	24	384	4.60	(2.8)	4.40	(2.9)					1.12	(0.73)	3.94	(1.4)	56	70	57
Twigg et al.	2017	YEAR	UK	2002	2009	24	725	5.80	(2.6)	4.50	(2.6)					1.27	(0.75)	4.70	(1.5)	58	67	70
van der Leeden et al.	2010	EAC	Netherlands	1995	2007	96	845	50.82	(25)							1.21	(0.76)	5.20	(1.2)	55	69	51
Wechalekar et al.	2016	Adelaide EAC Cohort	Australia	2000	2014	36	263									0.76	(0.55)			55	71	60
West et al.	2009	Umea Cohort	Sweden	1996	1998	72	50					33.10	(11.5)	48.40	(10.1)					51	68	92
Westhoff et al.	2008	German Cohort	Germany	2000	2001	36	916	4.30	(2.6)									4.79	(1.5)	57	70	
Wolfe et al.	1998	Withita Cohort	USA	1973	1993	228	256									0.89	(0.7)			52	73	74

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Section 1. Identifying Information

1. Given Name (First Name): Lewis
2. Surname (Last Name): Carpenter
3. Date: 2/14/2019

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title: Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal

6. Manuscript Identifying Number (if you know it): SAR-2019-77

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If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

MQ/ARUK	☑	☐	☐	☐	MQ16IP18	× ADD

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Section 1. Identifying Information

1. Given Name (First Name) | 2. Surname (Last Name) | 3. Date

David | Scott | 2/14/2010

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title

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National Institutes For Health Research	☑	☐	☐	☐	NIHR Programme Grant	×

ADD

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James | Gwinnutt | 2/14/2019

4. Are you the corresponding author? ☐ Yes ☑ No

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Section 1. Identifying Information

1. Given Name (First Name): Praveen
2. Surname (Last Name): Mahendran
3. Date: 2/14/2010

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title: Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal

6. Manuscript Identifying Number (if you know it): SAR-2010-77

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Rosemarie | Barnett | 2/19/2019

4. Are you the corresponding author? ☐ Yes ☑ No

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1. Given Name (First Name): Sam
2. Surname (Last Name): Norton
3. Date: 2/14/2010

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title: Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal

6. Manuscript Identifying Number (if you know it): SAR-2010-77

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Are there any relevant conflicts of interest? ☑ Yes ☐ No

If yes, please fill out the appropriate information below. If you have more than one entity press the "ADD" button to add a row. Excess rows can be removed by pressing the "X" button.

MQ/ARUK	☑	☐	☐	☐	MQ16IP18	× ADD

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ELENA | NIKIPHOROU | 6/3/2019

4. Are you the corresponding author? ☐ Yes ☑ No

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SAR-2019-77

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1. Given Name (First Name): Suzanne
2. Surname (Last Name): Verstappen
3. Date: 2/14/2010

4. Are you the corresponding author? ☐ Yes ☑ No

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2/3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5/6 + Supplementary Material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6/7 + Supplementary Material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6/7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5/6 + Supplementary material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7/8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Material

Search terms

rheumatoid arthritis
observational
observational study
observational method
observational cohort
longitudinal studies
prospective
epidemiologic studies
epidemiologic study
epidemiological research
longitudinal
cohort analysis
prospective study
epidemiological data
pain
chronic pain
pain assessment
inflammatory pain
pain measurement
chronic inflammatory pain
musculoskeletal pain
PAIN MANAGEMENT
analgesia
Fatigue
Fatigue Impact Scale
Fatigue Severity Scale
Depression
Depression Anxiety Stress Scale
mixed anxiety and depression
Beck Depression Inventory
depression assessment
Self-rating Depression Scale
Hospital Anxiety and Depression Scale
depression inventory
experimental depression test
MAJOR DEPRESSION
RECURRENT DEPRESSION
TREATMENT RESISTANT DEPRESSION
Anxiety
anxiety disorder
Beck Anxiety Inventory
anxiety assessment
experimental anxiety test
generalized anxiety disorder
mixed anxiety and depression
Self-rating Anxiety Scale
GENERALIZED ANXIETY DISORDER
ANXIETY SENSITIVITY
ANXIETY MANAGEMENT
Distress
Coping Behaviour
mental health
mental wellbeing
psychological well-being
Well Being

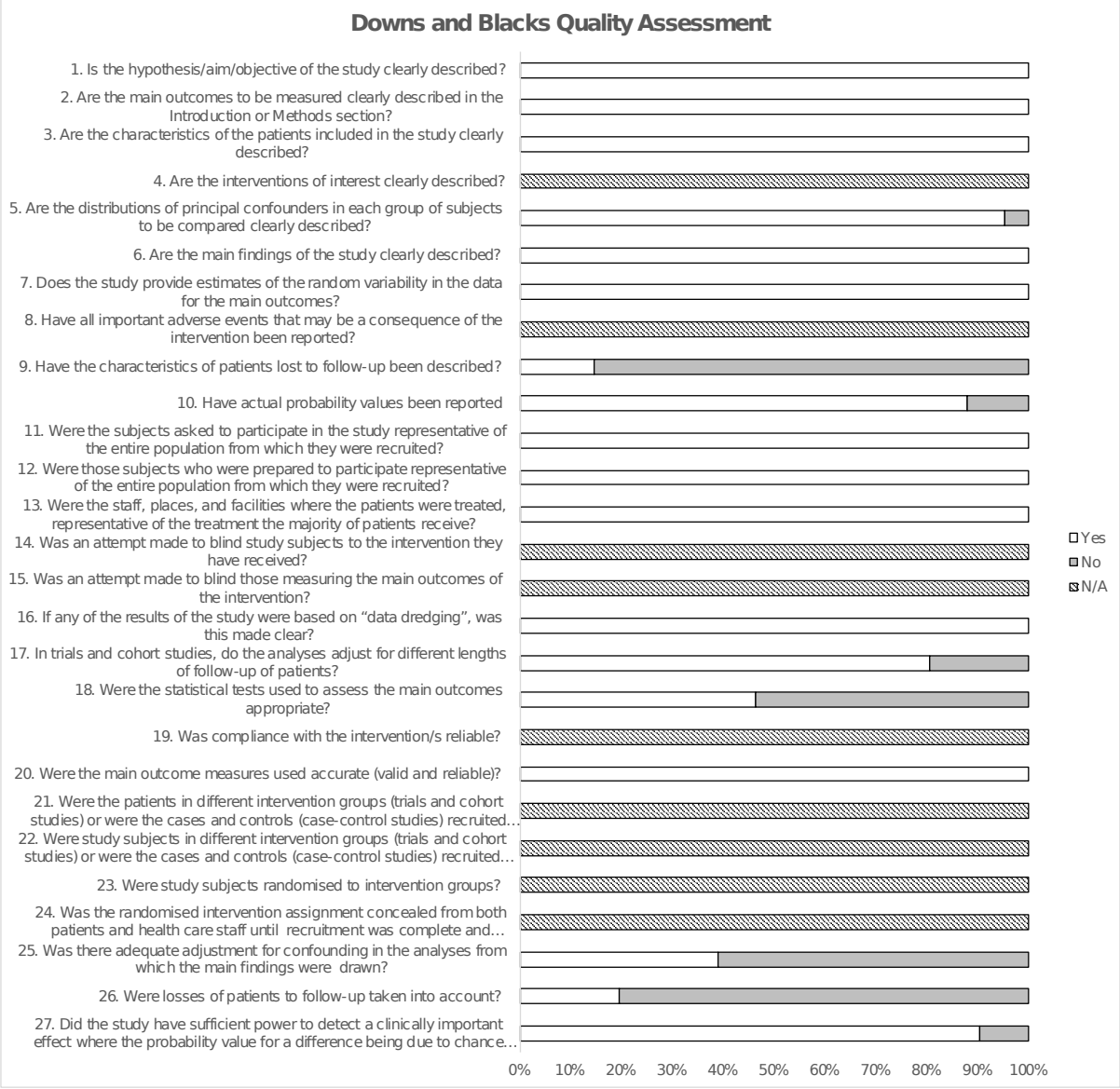
affective disturbance
Affective Disorders
psychological distress
vitality
short form 36
short-form 36
SF-36
Short Form-36
quality of life
vitality
Physical Activity
Activities of Daily Living

NOT

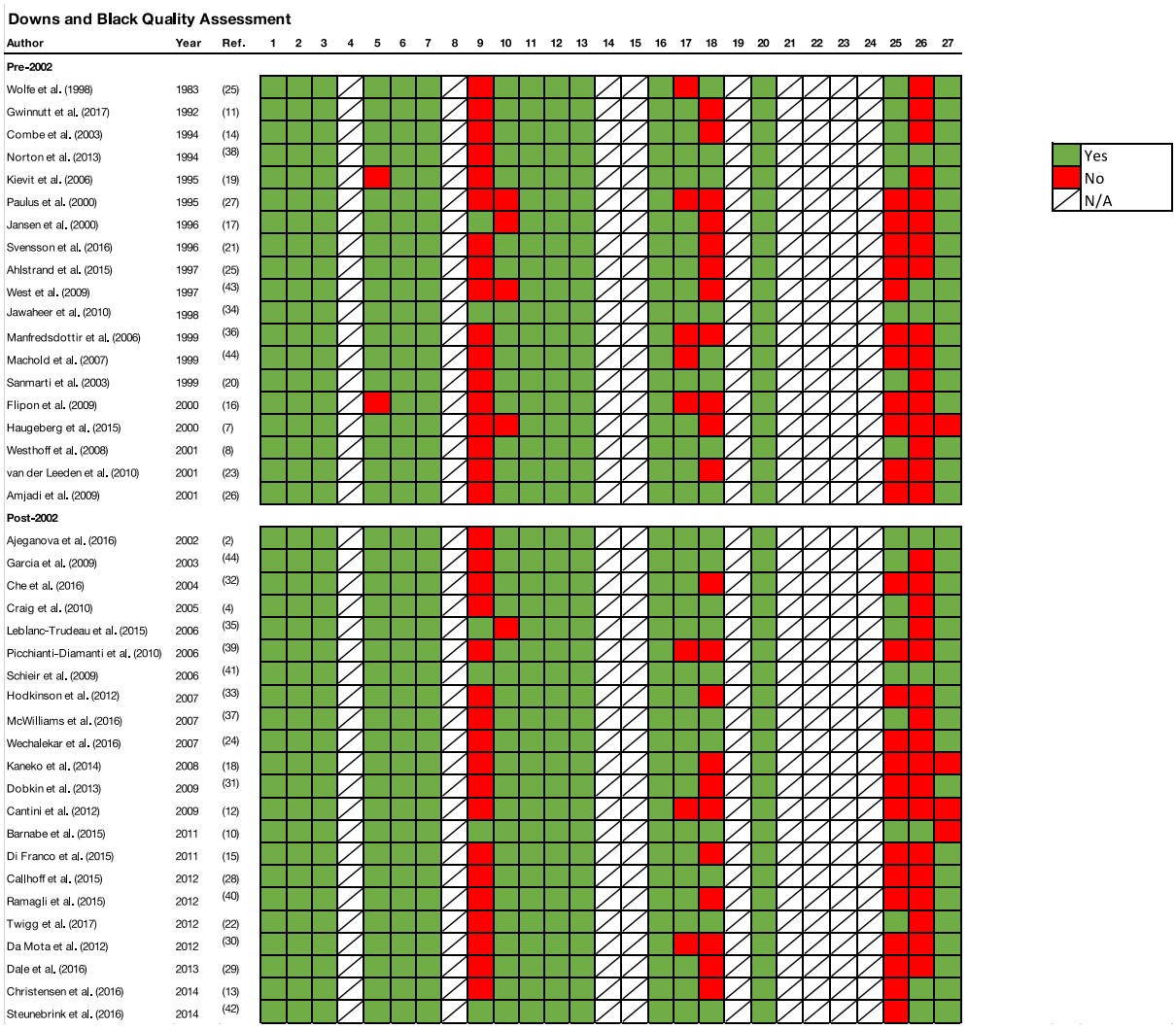
trial
clinical trial
randomised clinical trial
randomized clinical trial

(((((rheumatoid arthritis) OR arthritis, rheumatoid[MeSH Terms]) OR rheumatoid arthritis[MeSH Terms])) AND ((((((((((observational) OR longitudinal) OR longitudinal studies) OR longitudinal study) OR prospective) OR prospective study) OR epidemiologic study) OR epidemiological research) OR longitudinal studies[MeSH Terms]) OR design, epidemiological research[MeSH Terms])) AND ((((((((((((((((((((pain) OR assessment, pain[MeSH Terms]) OR chronic pain) OR fatigue) OR fatigue[MeSH Terms]) OR depression) OR depression[MeSH Terms]) OR anxiety) OR anxiety[MeSH Terms]) OR mental health) OR association, mental health[MeSH Terms]) OR mental wellbeing) OR vitality) OR distress) OR psychological distress) OR affective disorder) OR short-form-36) OR quality of life[MeSH Terms]) OR quality of life) OR SF-36) NOT ((((trial[Title]) OR clinical trial[Title]) OR randomised controlled trial[Title]) OR randomized controlled trial[Title])

Downs and Blacks Quality Assessment



Proportion of studies answering yes, no and N/A to the 27 items of the Downs and Blacks quality assessment tool. Items 4, 8, 12, 14, 15, 29, 21, 22, 23 & 24 were not completed since they asked about trial procedures.

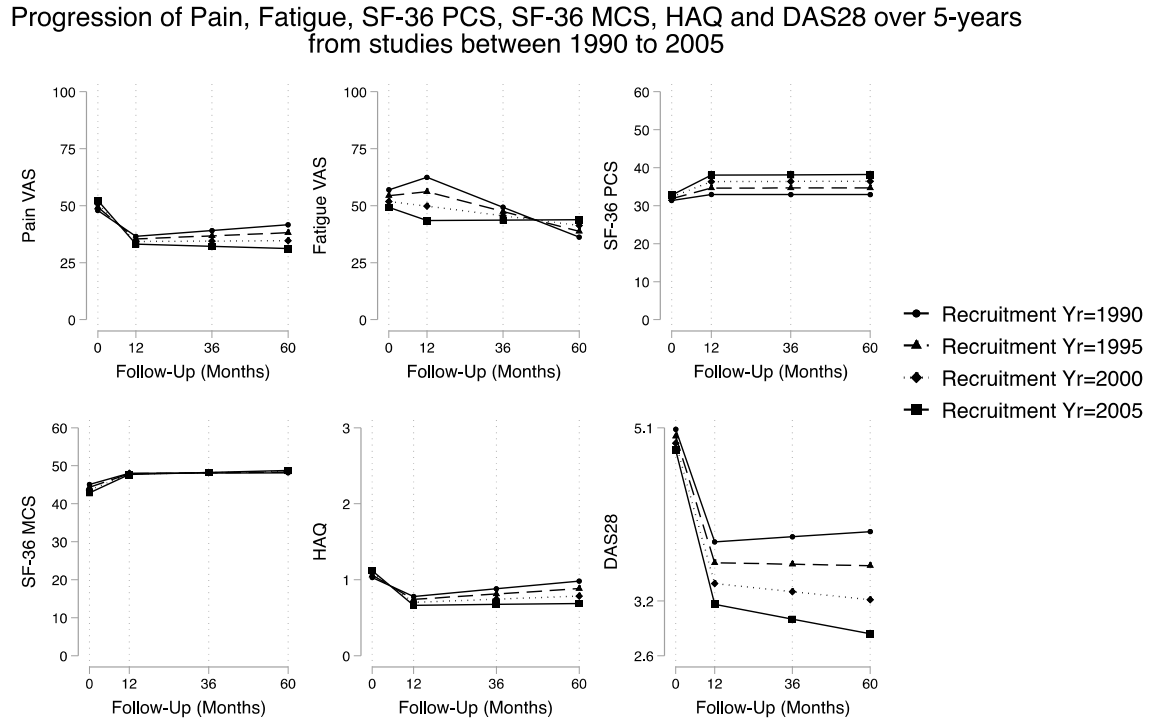


A table to illustrate which items each study were reported as satisfying (green) or not satisfying (red) for each of the items of the Downs and Blacks quality assessment tool. Items 4, 8, 12, 14, 15, 29, 21, 22, 23 & 24 were not completed since they asked about trial procedures.

Sensitivity Analysis looking at recruitment year as a continuous outcome

A sensitivity analysis was conducted to investigate whether there was a linear association between the studies year of recruitment with the progression of each outcome over the follow-up period. Rather than including recruitment year as a binary outcome, it was entered in the mixed effects model as a continuous outcome, along with an interaction effect with follow-up period.

The model estimated means of each outcome over the 60-month follow-up at 5-year intervals for recruitment year (1990, 1995, 2000 and 2005) are presented in the figure below. Each line represents the model estimated means for those specific recruitment years.



Supplementary Figure 1 - Estimated marginal means for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month with year of recruitment expressed as a continuous measure. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Circle points with solid black lines indicate the estimated means for cohorts in 1990, triangle points with a dashed black line indicate the estimated means for cohorts in 1995, diamond points with dotted black line indicate the estimated means for cohorts in 2000 and square points with solid black line indicated estimated means for cohorts in 2005. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

The models demonstrated a statistically significant main effect of recruitment year for the DAS-28, showing a reduction of -0.03 (95% Confidence Intervals -0.05 to -0.01, $p<0.05$). However, the estimated effect of recruitment year was non-significant for HAQ (-0.003, 95% CI's -0.01 to 0.01), SF36 MCS (-0.04, 95% CI's -0.43 to 0.34), SF-36 PCS (0.25, 95% CI's -0.07 to 0.57), fatigue (-0.54, 95% CI's -1.35 to 0.27) and pain (-0.04, 95% CI's -0.44 to 0.36).

The linear association corroborates with the main analysis looking at recruitment year as a dichotomous outcome.

Sensitivity Analysis looking at the Disease Activity Score-28 (DAS28) component scores – Swollen Joint Count-28 (SJC-28), Tender Joint Count-28 (TJC-28), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR).

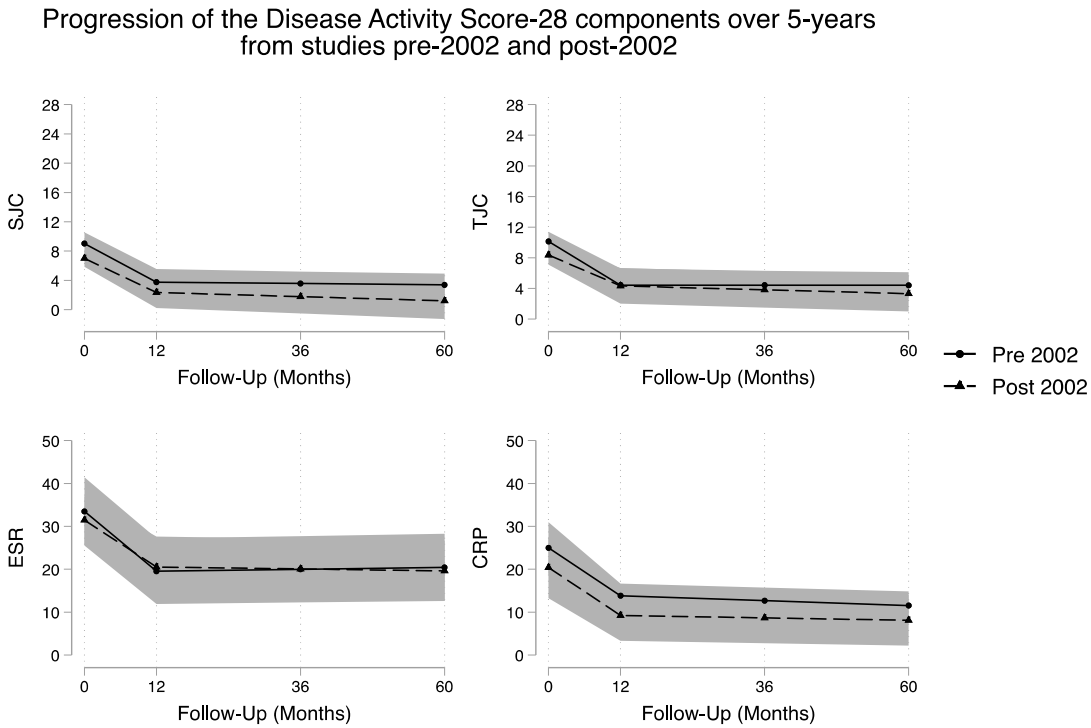
Additional sensitivity analysis was conducted to investigate the progression of the sub-components of the Disease Activity Score-28 (DAS28), which included the Swollen Joint Count (SJC), Tender Joint Count (TJC) and acute phase markers: C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Of the 37 cohorts that had reported DAS28, 30 had data on the SJC, 27 had data on TJC, 18 had data on ESR and 22 had data on CRP. The 28-joint count version of the SJC and TJC was the more prominent measure used, with 25 (83%) of the 30 cohorts reporting the SJC-28 and 23 (85%) of the 27 cohorts reporting the TJC-28. Given the complexities in combining joint counts of different maximum scores, this sensitivity analysis focuses only on the SJC-28 and the TJC-28.

Mixed-effects models indicate a statistically significant improvements in SJC-28 at baseline for cohorts recruiting patients post-2002 compared to those recruiting patients pre-2002, with a Mean Difference (MD) of 2.02 (95% Confidence Intervals (CI) -3.94 to -0.10, P<0.05). This improvement remained relatively stable over the course of the follow-up, however the decreased precision results in statistically non-significant effects, indicating MD scores in favour of post-2002 cohorts at 1.41 (95% CIs -4.19 to 1.38), 1.79 (95% CIs -4.61 to 1.02) and 2.18 (95% CIs -5.10 to 0.74, P<0.05) at the 12, 36 and 60-month follow-up periods.

Similarly, there was some evidence of a decreased level of TJC-28 between those cohorts recruiting patients post-2002 and those recruiting patients pre-2002 at baseline, with a statistically significant MD score of -1.78 (95% CIs -3.55 to -0.02), however the MD estimates reduced in months 12 (-0.10; 95% CIs -3.29 to 3.10) and 36 (-0.60; 95% CIs -3.59 to 2.39), but increased to similar levels at baseline by month 60 (-1.10; 95% CIs -3.98 to 1.78). However, imprecision of the point estimates led to large uncertainty and statistical non-significance of these estimates.

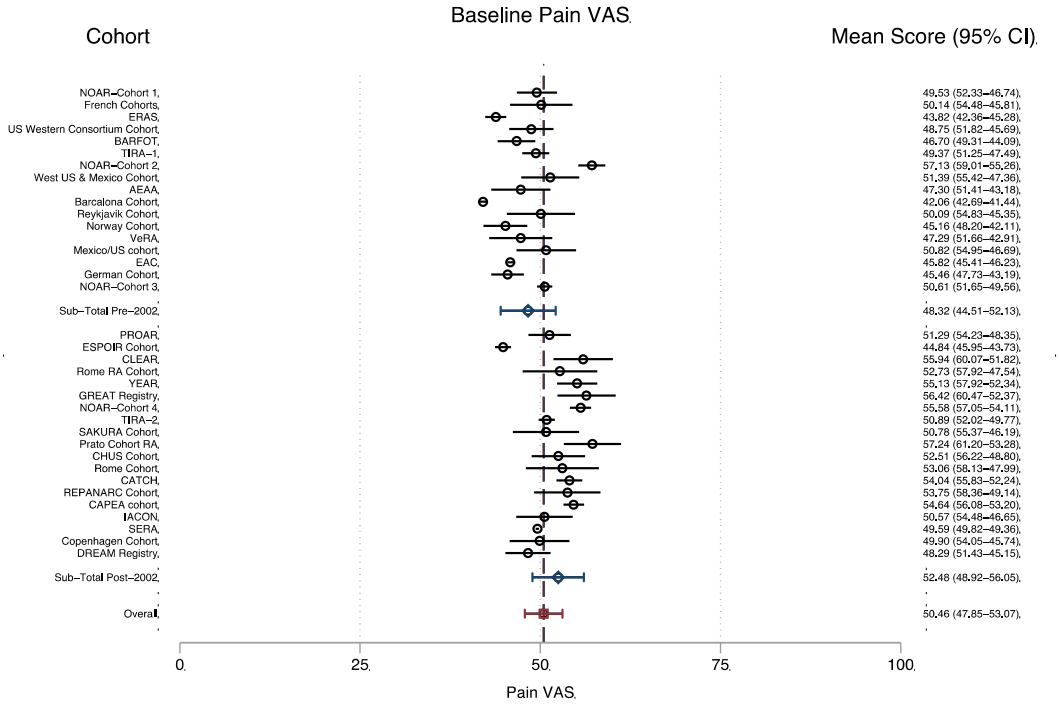
Whereas estimates for ESR demonstrated little difference between the pre- and post-2002 cohorts, with very small, statistically non-significant MD estimates at baseline (-2.02; 95% CIs -11.72 to 7.67), 12 (0.98; 95% CIs -9.47 to 11.42), 36 (0.08; 95% CIs -10.39 to 10.56) and 60 (-0.81; 95% CIs -11.32 to 9.71), CRP demonstrated a more consistent, albeit statistically non-significant, effect from baseline to month 60, with improved CRP scores at the baseline, 12, 36 and 60-month time points of 4.60 (95% CIs -13.92 to 4.72), 4.60 (95% CIs -11.18 to 1.97), 4.02 (95% CIs -10.66 to 2.62) and 3.43 (95% CIs -10.22 to 3.35) for the post-2002 cohorts relative to the pre-2002 cohort. However, low numbers of data points, particularly at the later follow-up time-points, led to large imprecision around these estimates.

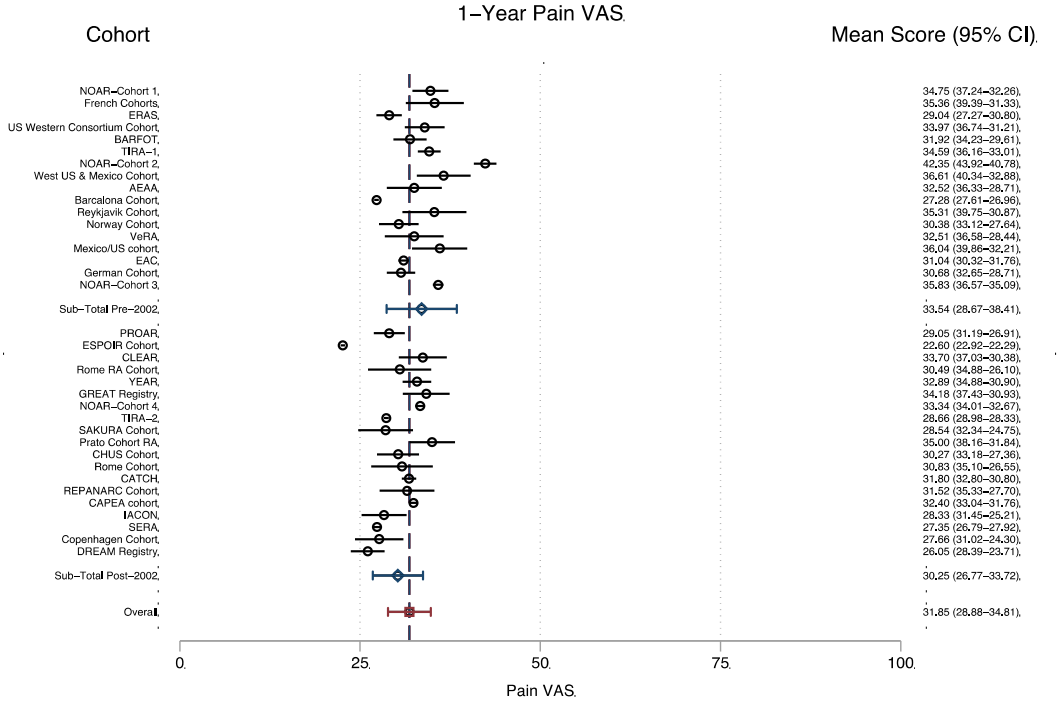
The estimates for both the SJC-28, TJC-28, ESR and CRP outcomes over the 60-month follow-up period for both pre and post-2002 cohorts are presented graphically in Supplementary Figure 1.

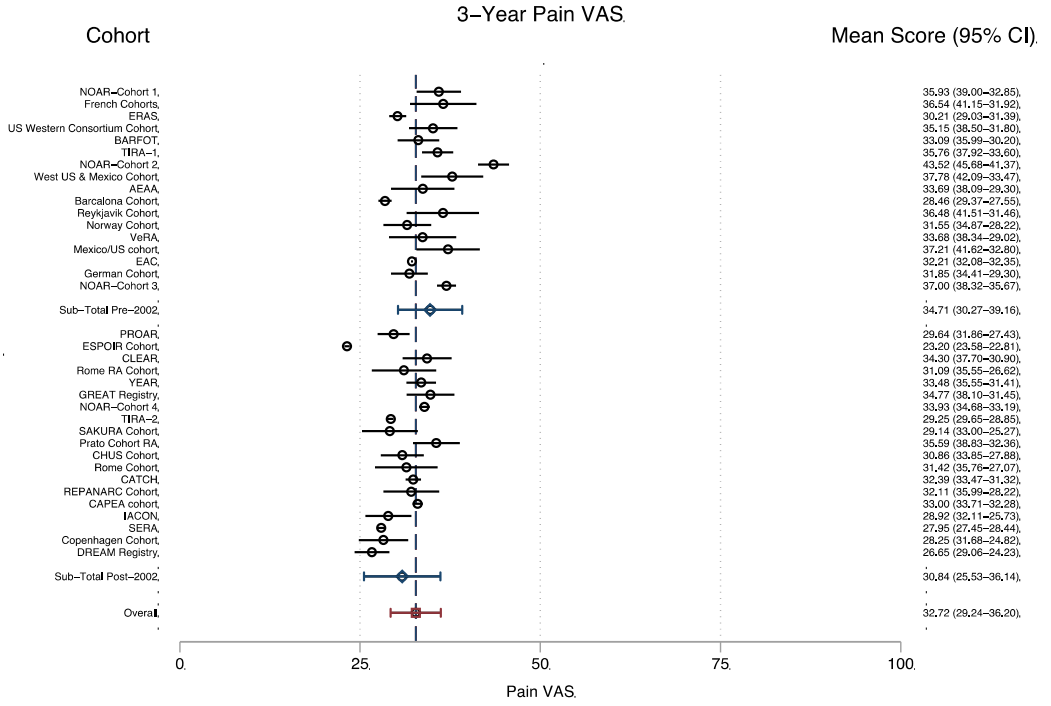


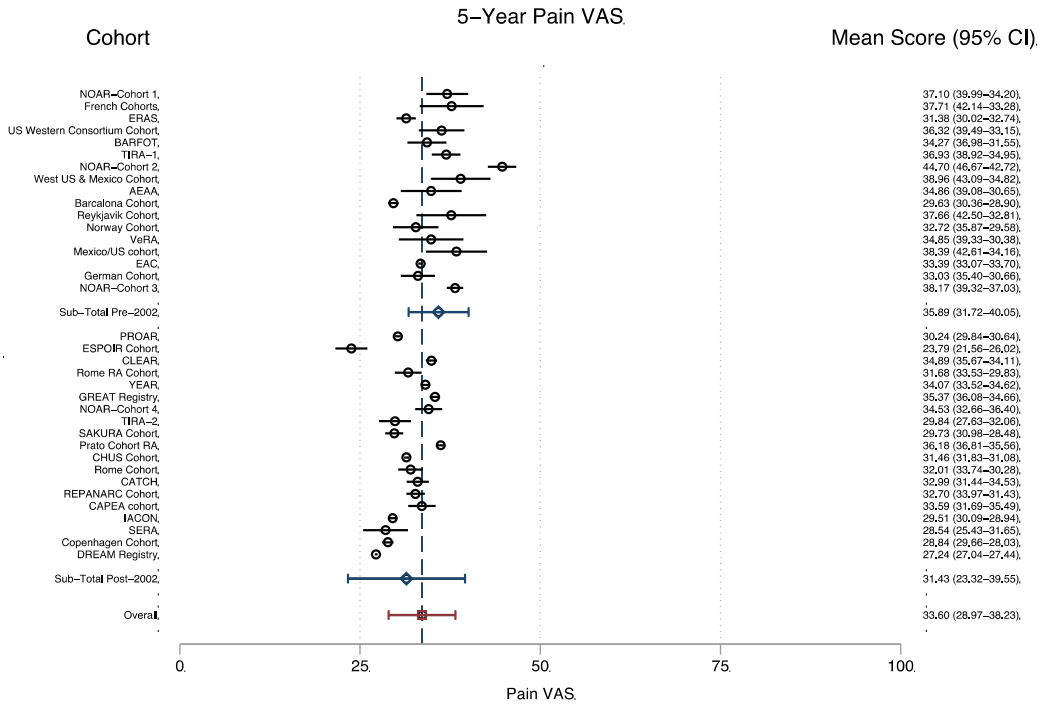
Supplementary Figure 2 - Estimated marginal means for the Swollen Joint Count (SJC), Tender Joint Count (TJC), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) outcomes at baseline, 12, 36 and 60-month time-points. The Joint counts are scored out of 28. Circle points with solid black lines indicate the estimated means for the pre-2002 cohorts, whilst triangle points with a dashed black line indicate the estimated means for the post-2002 cohorts. 95% Confidence Intervals are indicated by the grey shaded areas.

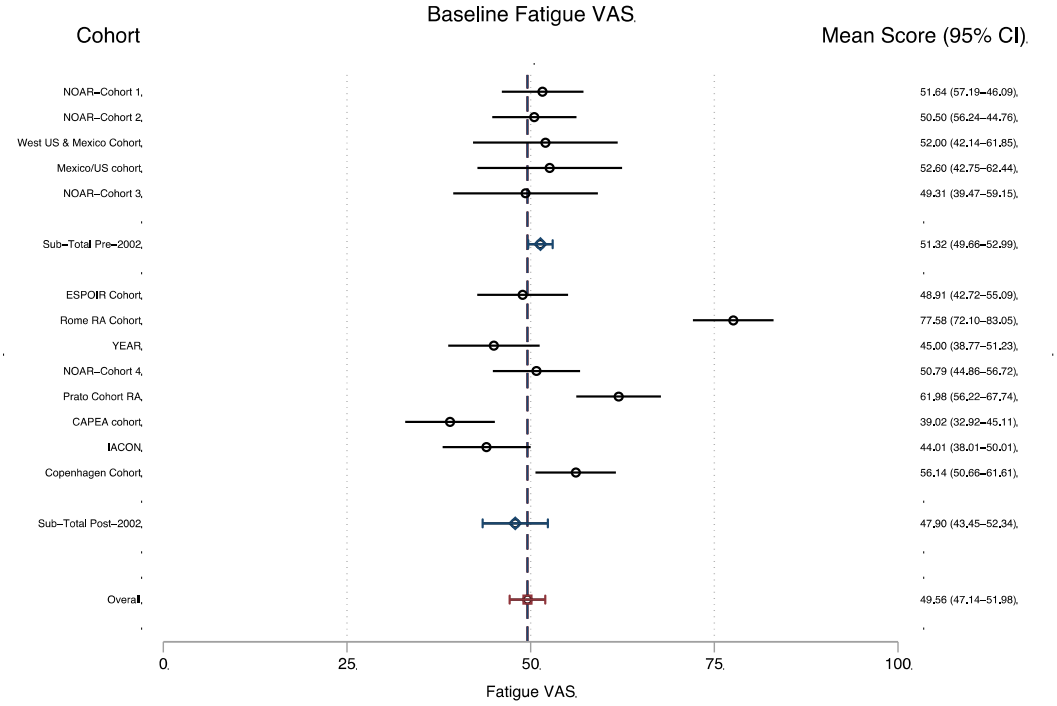
Forest plots of each outcome at baseline, 1, 3 and 5-year follow-up from all cohort studies included in the review

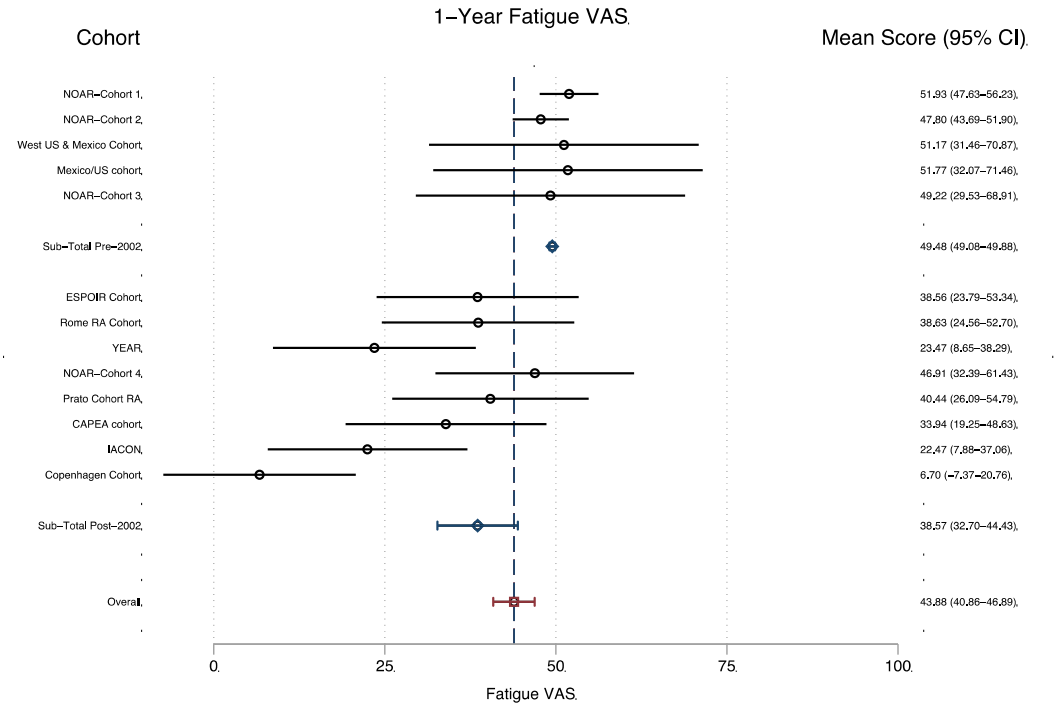


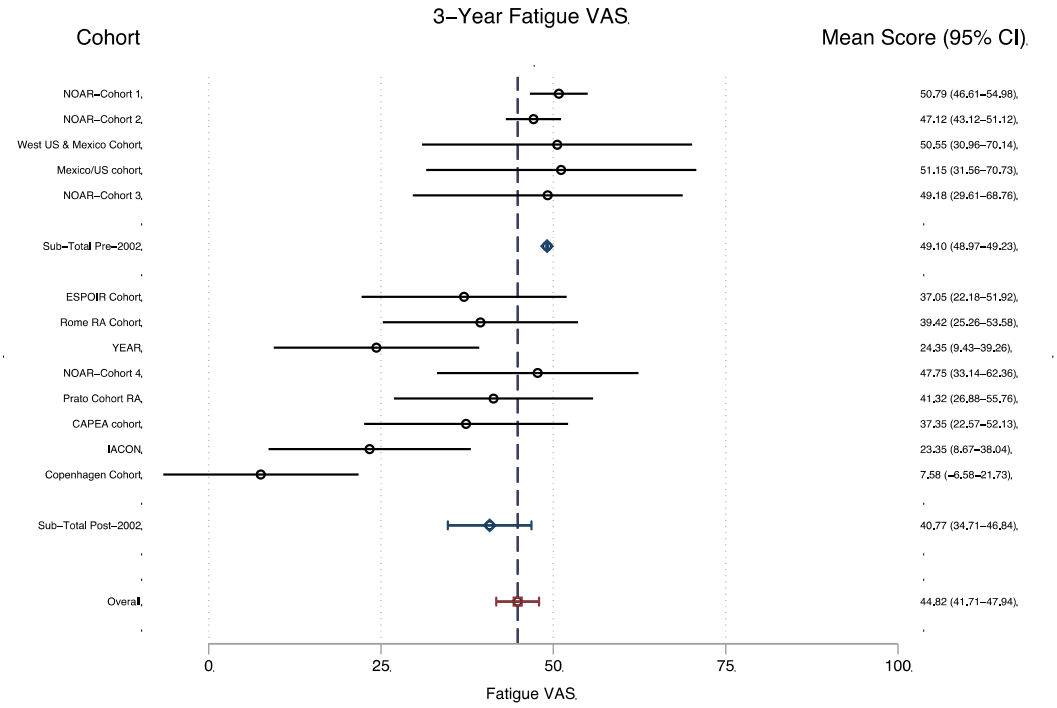


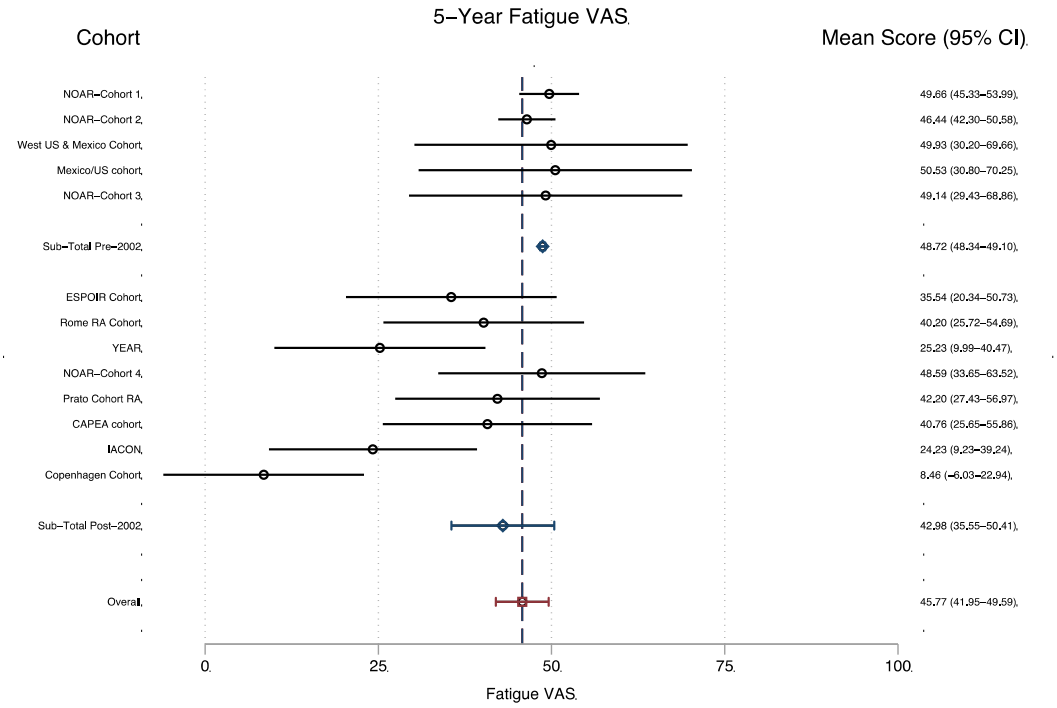

3–Year Pain VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 35.93 (39.00–32.85)
French Cohorts, 36.54 (41.15–31.92)
ERAS, 30.21 (29.03–31.39)
US Western Consortium Cohort, 35.15 (38.50–31.80)
BARFOT, 33.09 (35.99–30.20)
TIRA–1, 35.76 (37.92–33.60)
NOAR–Cohort 2, 43.52 (45.68–41.37)
West US & Mexico Cohort, 37.78 (42.09–33.47)
AEAA, 33.69 (38.09–29.30)
Barcalona Cohort, 28.46 (29.37–27.55)
Reykjavik Cohort, 36.48 (41.51–31.46)
Norway Cohort, 31.55 (34.87–28.22)
VeRA, 33.68 (38.34–29.02)
Mexico/US cohort, 37.21 (41.62–32.80)
EAC, 32.21 (32.08–32.35)
German Cohort, 31.85 (34.41–29.30)
NOAR–Cohort 3, 37.00 (38.32–35.67)
Sub–Total Pre–2002, 34.71 (30.27–39.16)
PROAR, 29.64 (31.86–27.43)
ESPOIR Cohort, 23.20 (23.58–22.81)
CLEAR, 34.30 (37.70–30.90)
Rome RA Cohort, 31.09 (35.55–26.62)
YEAR, 33.48 (35.55–31.41)
GREAT Registry, 34.77 (38.10–31.45)
NOAR–Cohort 4, 33.93 (34.68–33.19)
TIRA–2, 29.25 (29.65–28.85)
SAKURA Cohort, 29.14 (33.00–25.27)
Prato Cohort RA, 35.59 (38.83–32.36)
CHUS Cohort, 30.86 (33.85–27.88)
Rome Cohort, 31.42 (35.76–27.07)
CATCH, 32.39 (33.47–31.32)
REPANARC Cohort, 32.11 (35.99–28.22)
CAPEA cohort, 33.00 (33.71–32.28)
IACON, 28.92 (32.11–25.73)
SERA, 27.95 (27.45–28.44)
Copenhagen Cohort, 28.25 (31.68–24.82)
DREAM Registry, 26.65 (29.06–24.23)
Sub–Total Post–2002, 30.84 (25.53–36.14)
Overall, 32.72 (29.24–36.20)
0
25
50
75
100
Pain VAS

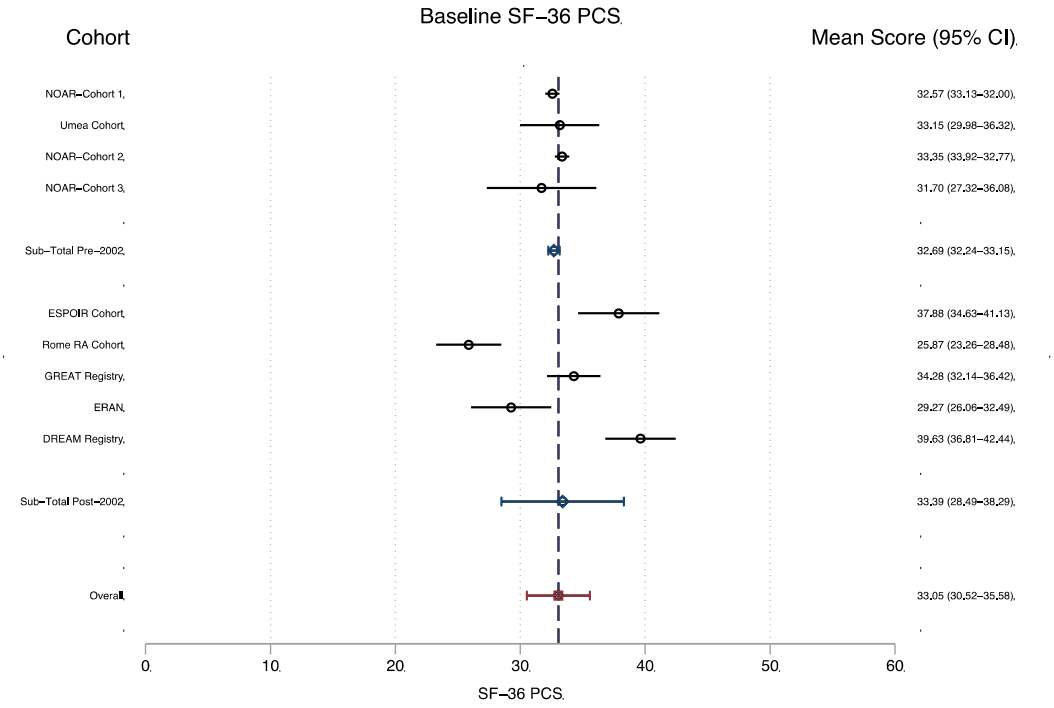

5–Year Pain VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 37.10 (39.99–34.20)
French Cohorts, 37.71 (42.14–33.28)
ERAS, 31.38 (30.02–32.74)
US Western Consortium Cohort, 36.32 (39.49–33.15)
BARFOT, 34.27 (36.98–31.55)
TIRA–1, 36.93 (38.92–34.95)
NOAR–Cohort 2, 44.70 (46.67–42.72)
West US & Mexico Cohort, 38.96 (43.09–34.82)
AEAA, 34.86 (39.08–30.65)
Barcalona Cohort, 29.63 (30.36–28.90)
Reykjavik Cohort, 37.66 (42.50–32.81)
Norway Cohort, 32.72 (35.87–29.58)
VeRA, 34.85 (39.33–30.38)
Mexico/US cohort, 38.39 (42.61–34.16)
EAC, 33.39 (33.07–33.70)
German Cohort, 33.03 (35.40–30.66)
NOAR–Cohort 3, 38.17 (39.32–37.03)
Sub–Total Pre–2002, 35.89 (31.72–40.05)
PROAR, 30.24 (29.84–30.64)
ESPOIR Cohort, 23.79 (21.56–26.02)
CLEAR, 34.89 (35.67–34.11)
Rome RA Cohort, 31.68 (33.53–29.83)
YEAR, 34.07 (33.52–34.62)
GREAT Registry, 35.37 (36.08–34.66)
NOAR–Cohort 4, 34.53 (32.66–36.40)
TIRA–2, 29.84 (27.63–32.06)
SAKURA Cohort, 29.73 (30.98–28.48)
Prato Cohort RA, 36.18 (36.81–35.56)
CHUS Cohort, 31.46 (31.83–31.08)
Rome Cohort, 32.01 (33.74–30.28)
CATCH, 32.99 (31.44–34.53)
REPANARC Cohort, 32.70 (33.97–31.43)
CAPEA cohort, 33.59 (31.69–35.49)
IACON, 29.51 (30.09–28.94)
SERA, 28.54 (25.43–31.65)
Copenhagen Cohort, 28.84 (29.66–28.03)
DREAM Registry, 27.24 (27.04–27.44)
Sub–Total Post–2002, 31.43 (23.32–39.55)
Overall, 33.60 (28.97–38.23)
0
25
50
75
100
Pain VAS

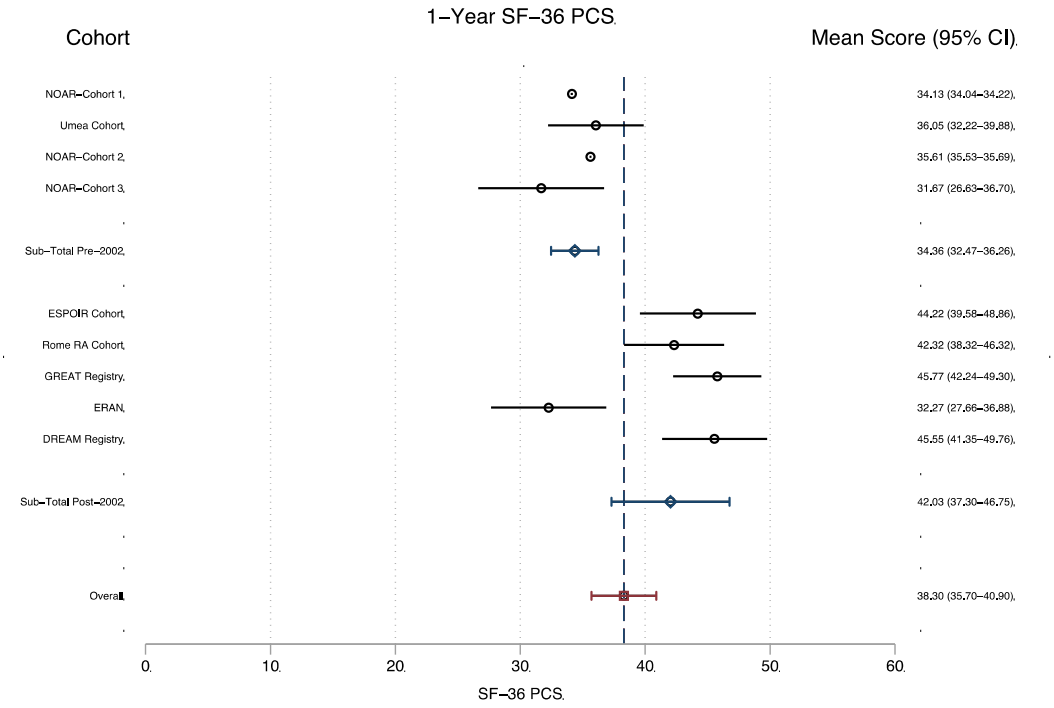

Baseline Fatigue VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 51.64 (57.19–46.09)
NOAR–Cohort 2, 50.50 (56.24–44.76)
West US & Mexico Cohort, 52.00 (42.14–61.85)
Mexico/US cohort, 52.60 (42.75–62.44)
NOAR–Cohort 3, 49.31 (39.47–59.15)
Sub–Total Pre–2002, 51.32 (49.66–52.99)
ESPOIR Cohort, 48.91 (42.72–55.09)
Rome RA Cohort, 77.58 (72.10–83.05)
YEAR, 45.00 (38.77–51.23)
NOAR–Cohort 4, 50.79 (44.86–56.72)
Prato Cohort RA, 61.98 (56.22–67.74)
CAPEA cohort, 39.02 (32.92–45.11)
IACON, 44.01 (38.01–50.01)
Copenhagen Cohort, 56.14 (50.66–61.61)
Sub–Total Post–2002, 47.90 (43.45–52.34)
Overall, 49.56 (47.14–51.98)
0
25
50
75
100
Fatigue VAS

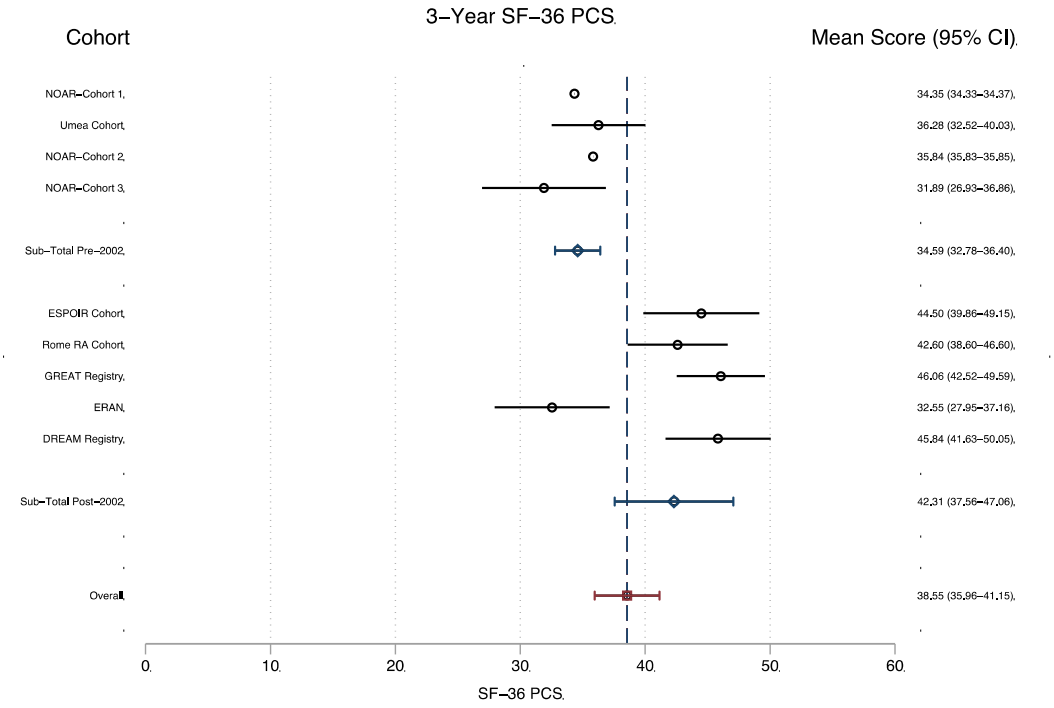

1–Year Fatigue VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 51.93 (47.63–56.23)
NOAR–Cohort 2, 47.80 (43.69–51.90)
West US & Mexico Cohort, 51.17 (31.46–70.87)
Mexico/US cohort, 51.77 (32.07–71.46)
NOAR–Cohort 3, 49.22 (29.53–68.91)
Sub–Total Pre–2002, 49.48 (49.08–49.88)
ESPOIR Cohort, 38.56 (23.79–53.34)
Rome RA Cohort, 38.63 (24.56–52.70)
YEAR, 23.47 (8.65–38.29)
NOAR–Cohort 4, 46.91 (32.39–61.43)
Prato Cohort RA, 40.44 (26.09–54.79)
CAPEA cohort, 33.94 (19.25–48.63)
IACON, 22.47 (7.88–37.06)
Copenhagen Cohort, 6.70 (–7.37–20.76)
Sub–Total Post–2002, 38.57 (32.70–44.43)
Overall, 43.88 (40.86–46.89)
0
25
50
75
100
Fatigue VAS

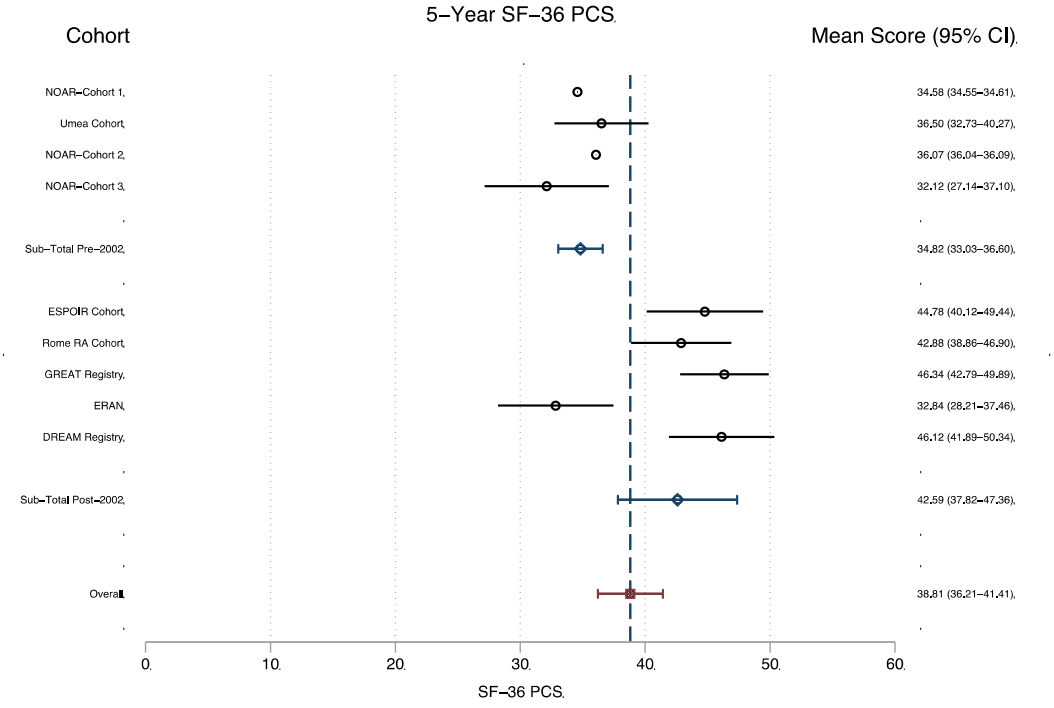

3–Year Fatigue VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1
NOAR–Cohort 2
West US & Mexico Cohort
Mexico/US cohort
NOAR–Cohort 3
Sub–Total Pre–2002
ESPOIR Cohort
Rome RA Cohort
YEAR
NOAR–Cohort 4
Prato Cohort RA
CAPEA cohort
IACON
Copenhagen Cohort
Sub–Total Post–2002
Overall
50.79 (46.61–54.98)
47.12 (43.12–51.12)
50.55 (30.96–70.14)
51.15 (31.56–70.73)
49.18 (29.61–68.76)
49.10 (48.97–49.23)
37.05 (22.18–51.92)
39.42 (25.26–53.58)
24.35 (9.43–39.26)
47.75 (33.14–62.36)
41.32 (26.88–55.76)
37.35 (22.57–52.13)
23.35 (8.67–38.04)
7.58 (–6.58–21.73)
40.77 (34.71–46.84)
44.82 (41.71–47.94)
0
25
50
75
100
Fatigue VAS

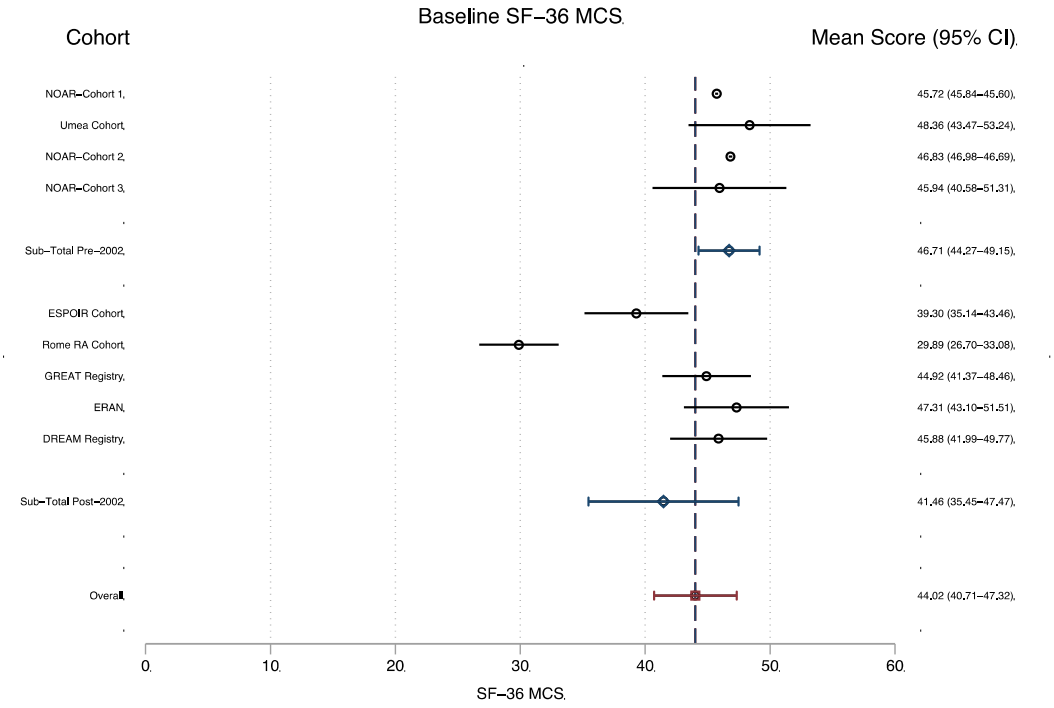

5–Year Fatigue VAS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1
NOAR–Cohort 2
West US & Mexico Cohort
Mexico/US cohort
NOAR–Cohort 3
Sub–Total Pre–2002
ESPOIR Cohort
Rome RA Cohort
YEAR
NOAR–Cohort 4
Prato Cohort RA
CAPEA cohort
IACON
Copenhagen Cohort
Sub–Total Post–2002
Overall
49.66 (45.33–53.99)
46.44 (42.30–50.58)
49.93 (30.20–69.66)
50.53 (30.80–70.25)
49.14 (29.43–68.86)
48.72 (48.34–49.10)
35.54 (20.34–50.73)
40.20 (25.72–54.69)
25.23 (9.99–40.47)
48.59 (33.65–63.52)
42.20 (27.43–56.97)
40.76 (25.65–55.86)
24.23 (9.23–39.24)
8.46 (–6.03–22.94)
42.98 (35.55–50.41)
45.77 (41.95–49.59)
0
25
50
75
100
Fatigue VAS

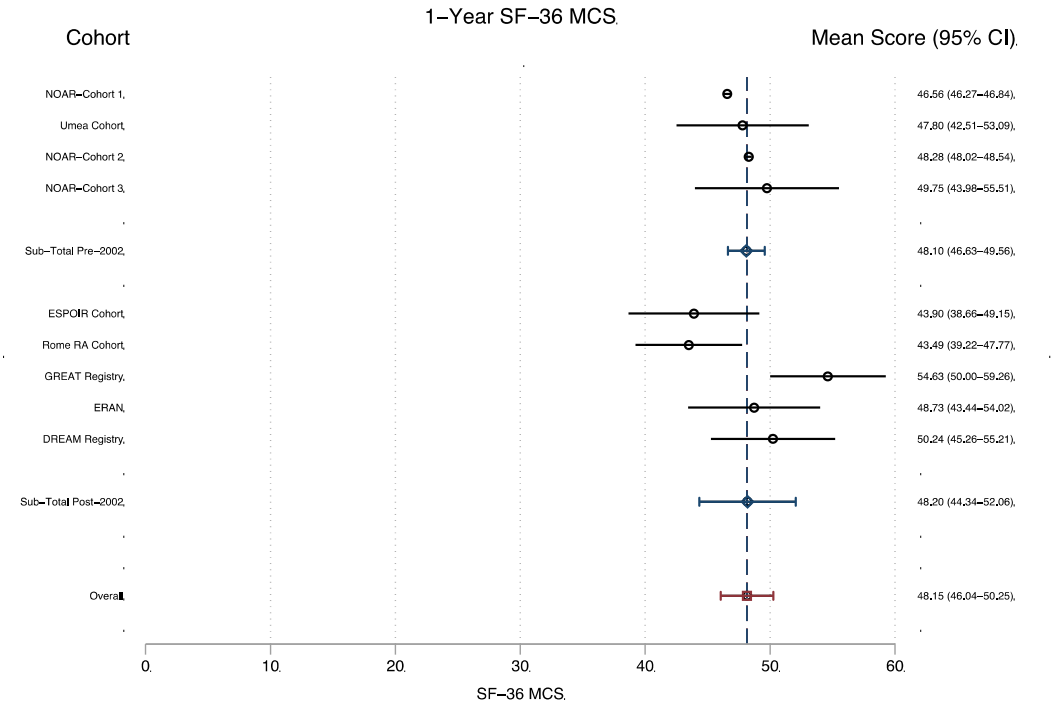

Baseline SF−36 PCS
Cohort
Mean Score (95% CI)
NOAR−Cohort 1, 32.57 (33.13−32.00),
Umea Cohort, 33.15 (29.98−36.32),
NOAR−Cohort 2, 33.35 (33.92−32.77),
NOAR−Cohort 3, 31.70 (27.32−36.08),
Sub−Total Pre−2002, 32.69 (32.24−33.15),
ESPOIR Cohort, 37.88 (34.63−41.13),
Rome RA Cohort, 25.87 (23.26−28.48),
GREAT Registry, 34.28 (32.14−36.42),
ERAN, 29.27 (26.06−32.49),
DREAM Registry, 39.63 (36.81−42.44),
Sub−Total Post−2002, 33.39 (28.49−38.29),
Overall, 33.05 (30.52−35.58),
0.
10.
20.
30.
40.
50.
60.
SF−36 PCS.

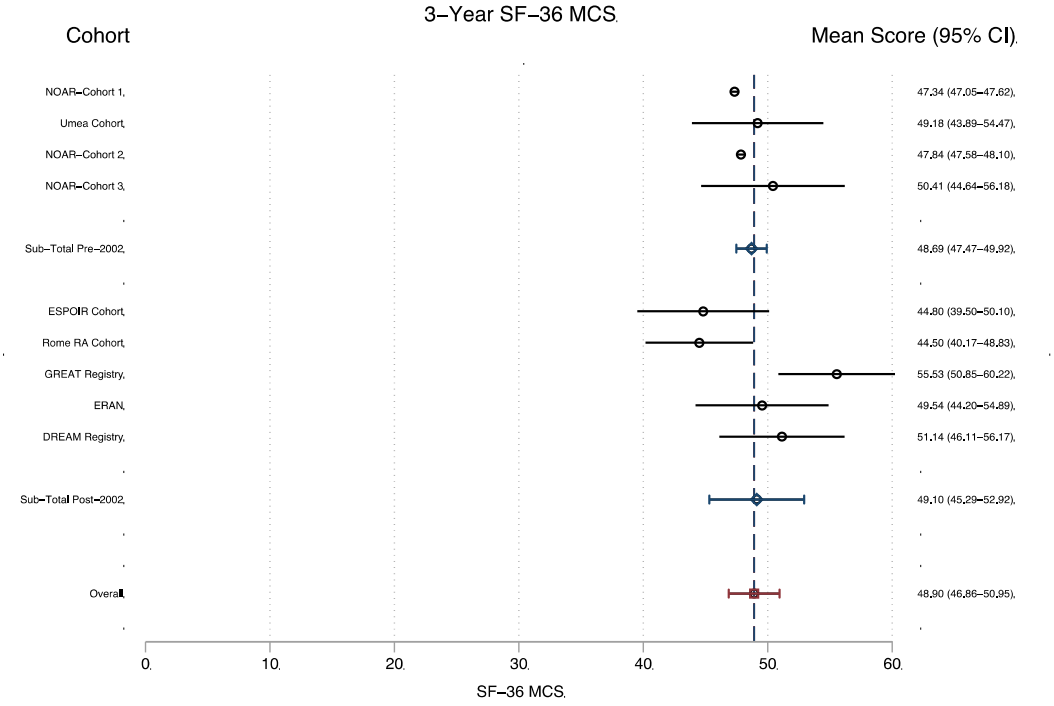

1−Year SF−36 PCS
Cohort
Mean Score (95% CI)
NOAR−Cohort 1, 34.13 (34.04−34.22),
Umea Cohort, 36.05 (32.22−39.88),
NOAR−Cohort 2, 35.61 (35.53−35.69),
NOAR−Cohort 3, 31.67 (26.63−36.70),
Sub−Total Pre−2002, 34.36 (32.47−36.26),
ESPOIR Cohort, 44.22 (39.58−48.86),
Rome RA Cohort, 42.32 (38.32−46.32),
GREAT Registry, 45.77 (42.24−49.30),
ERAN, 32.27 (27.66−36.88),
DREAM Registry, 45.55 (41.35−49.76),
Sub−Total Post−2002, 42.03 (37.30−46.75),
Overall, 38.30 (35.70−40.90),
0.
10.
20.
30.
40.
50.
60.
SF−36 PCS.

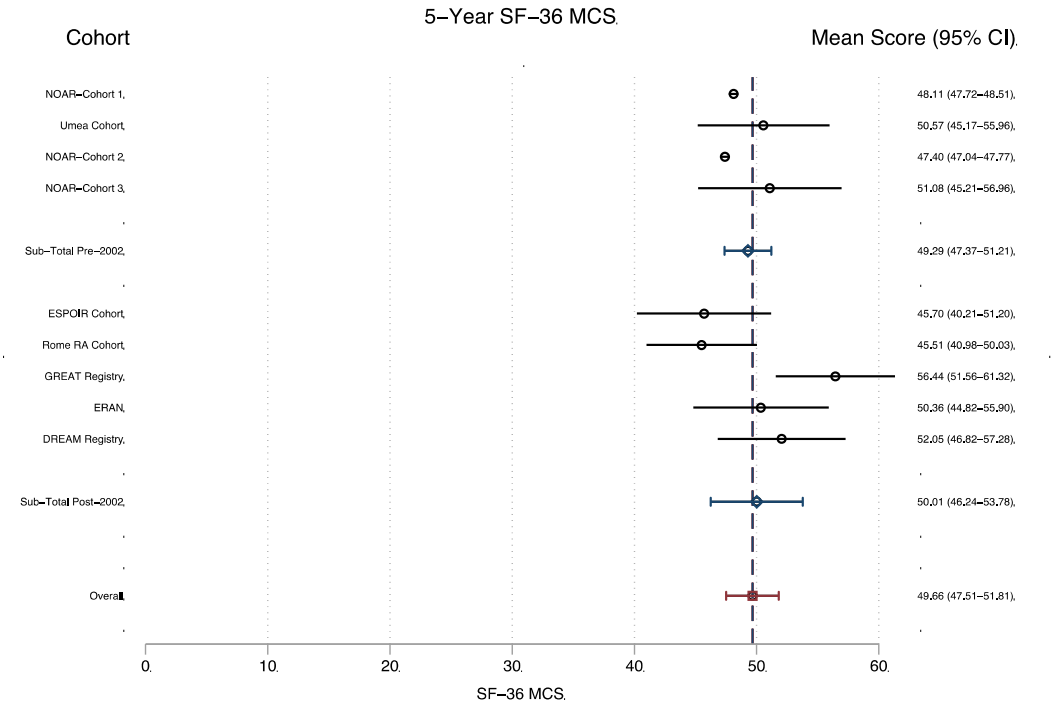

3–Year SF–36 PCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 34.35 (34.33–34.37)
Umea Cohort, 36.28 (32.52–40.03)
NOAR–Cohort 2, 35.84 (35.83–35.85)
NOAR–Cohort 3, 31.89 (26.93–36.86)
Sub–Total Pre–2002, 34.59 (32.78–36.40)
ESPOIR Cohort, 44.50 (39.86–49.15)
Rome RA Cohort, 42.60 (38.60–46.60)
GREAT Registry, 46.06 (42.52–49.59)
ERAN, 32.55 (27.95–37.16)
DREAM Registry, 45.84 (41.63–50.05)
Sub–Total Post–2002, 42.31 (37.56–47.06)
Overall, 38.55 (35.96–41.15)
0. 10. 20. 30. 40. 50. 60.
SF–36 PCS

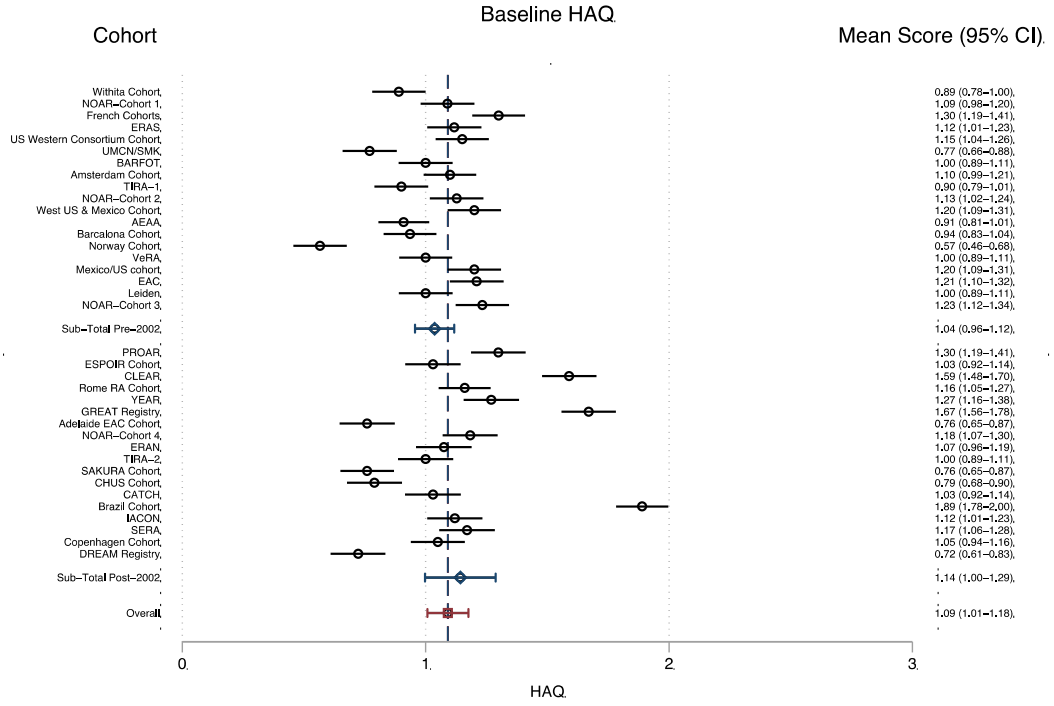

5–Year SF–36 PCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 34.58 (34.55–34.61)
Umea Cohort, 36.50 (32.73–40.27)
NOAR–Cohort 2, 36.07 (36.04–36.09)
NOAR–Cohort 3, 32.12 (27.14–37.10)
Sub–Total Pre–2002, 34.82 (33.03–36.60)
ESPOIR Cohort, 44.78 (40.12–49.44)
Rome RA Cohort, 42.88 (38.86–46.90)
GREAT Registry, 46.34 (42.79–49.89)
ERAN, 32.84 (28.21–37.46)
DREAM Registry, 46.12 (41.89–50.34)
Sub–Total Post–2002, 42.59 (37.82–47.36)
Overall, 38.81 (36.21–41.41)
0. 10. 20. 30. 40. 50. 60.
SF–36 PCS


Baseline SF–36 MCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 45.72 (45.84–45.60),
Umea Cohort, 48.36 (43.47–53.24),
NOAR–Cohort 2, 46.83 (46.98–46.69),
NOAR–Cohort 3, 45.94 (40.58–51.31),
Sub–Total Pre–2002, 46.71 (44.27–49.15),
ESPOIR Cohort, 39.30 (35.14–43.46),
Rome RA Cohort, 29.89 (26.70–33.08),
GREAT Registry, 44.92 (41.37–48.46),
ERAN, 47.31 (43.10–51.51),
DREAM Registry, 45.88 (41.99–49.77),
Sub–Total Post–2002, 41.46 (35.45–47.47),
Overall, 44.02 (40.71–47.32),
0.
10.
20.
30.
40.
50.
60.
SF–36 MCS.


1–Year SF–36 MCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 46.56 (46.27–46.84),
Umea Cohort, 47.80 (42.51–53.09),
NOAR–Cohort 2, 48.28 (48.02–48.54),
NOAR–Cohort 3, 49.75 (43.98–55.51),
Sub–Total Pre–2002, 48.10 (46.63–49.56),
ESPOIR Cohort, 43.90 (38.66–49.15),
Rome RA Cohort, 43.49 (39.22–47.77),
GREAT Registry, 54.63 (50.00–59.26),
ERAN, 48.73 (43.44–54.02),
DREAM Registry, 50.24 (45.26–55.21),
Sub–Total Post–2002, 48.20 (44.34–52.06),
Overall, 48.15 (46.04–50.25),
0.
10.
20.
30.
40.
50.
60.
SF–36 MCS.


3–Year SF–36 MCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 47.34 (47.05–47.62)
Umea Cohort, 49.18 (43.89–54.47)
NOAR–Cohort 2, 47.84 (47.58–48.10)
NOAR–Cohort 3, 50.41 (44.64–56.18)
Sub–Total Pre–2002, 48.69 (47.47–49.92)
ESPOIR Cohort, 44.80 (39.50–50.10)
Rome RA Cohort, 44.50 (40.17–48.83)
GREAT Registry, 55.53 (50.85–60.22)
ERAN, 49.54 (44.20–54.89)
DREAM Registry, 51.14 (46.11–56.17)
Sub–Total Post–2002, 49.10 (45.29–52.92)
Overall, 48.90 (46.86–50.95)
0. 10. 20. 30. 40. 50. 60.
SF–36 MCS.


5–Year SF–36 MCS
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 48.11 (47.72–48.51)
Umea Cohort, 50.57 (45.17–55.96)
NOAR–Cohort 2, 47.40 (47.04–47.77)
NOAR–Cohort 3, 51.08 (45.21–56.96)
Sub–Total Pre–2002, 49.29 (47.37–51.21)
ESPOIR Cohort, 45.70 (40.21–51.20)
Rome RA Cohort, 45.51 (40.98–50.03)
GREAT Registry, 56.44 (51.56–61.32)
ERAN, 50.36 (44.82–55.90)
DREAM Registry, 52.05 (46.82–57.28)
Sub–Total Post–2002, 50.01 (46.24–53.78)
Overall, 49.66 (47.51–51.81)
0. 10. 20. 30. 40. 50. 60.
SF–36 MCS.


Baseline HAQ
Cohort
Mean Score (95% CI)
Withita Cohort, 0.89 (0.78–1.00),
NOAR–Cohort 1, 1.09 (0.98–1.20),
French Cohorts, 1.30 (1.19–1.41),
ERAS, 1.12 (1.01–1.23),
US Western Consortium Cohort, 1.15 (1.04–1.26),
UMCN/SMK, 0.77 (0.66–0.88),
BARFOT, 1.00 (0.89–1.11),
Amsterdam Cohort, 1.10 (0.99–1.21),
TIRA–1, 0.90 (0.79–1.01),
NOAR–Cohort 2, 1.13 (1.02–1.24),
West US & Mexico Cohort, 1.20 (1.09–1.31),
AEAA, 0.91 (0.81–1.01),
Barcalona Cohort, 0.94 (0.83–1.04),
Norway Cohort, 0.57 (0.46–0.68),
VeRA, 1.00 (0.89–1.11),
Mexico/US cohort, 1.20 (1.09–1.31),
EAC, 1.21 (1.10–1.32),
Leiden, 1.00 (0.89–1.11),
NOAR–Cohort 3, 1.23 (1.12–1.34),
Sub–Total Pre–2002, 1.04 (0.96–1.12),
PROAR, 1.30 (1.19–1.41),
ESPOIR Cohort, 1.03 (0.92–1.14),
CLEAR, 1.59 (1.48–1.70),
Rome RA Cohort, 1.16 (1.05–1.27),
YEAR, 1.27 (1.16–1.38),
GREAT Registry, 1.67 (1.56–1.78),
Adelaide EAC Cohort, 0.76 (0.65–0.87),
NOAR–Cohort 4, 1.18 (1.07–1.30),
ERAN, 1.07 (0.96–1.19),
TIRA–2, 1.00 (0.89–1.11),
SAKURA Cohort, 0.76 (0.65–0.87),
CHUS Cohort, 0.79 (0.68–0.90),
CATCH, 1.03 (0.92–1.14),
Brazil Cohort, 1.89 (1.78–2.00),
IACON, 1.12 (1.01–1.23),
SERA, 1.17 (1.06–1.28),
Copenhagen Cohort, 1.05 (0.94–1.16),
DREAM Registry, 0.72 (0.61–0.83),
Sub–Total Post–2002, 1.14 (1.00–1.29),
Overall, 1.09 (1.01–1.18),
0.
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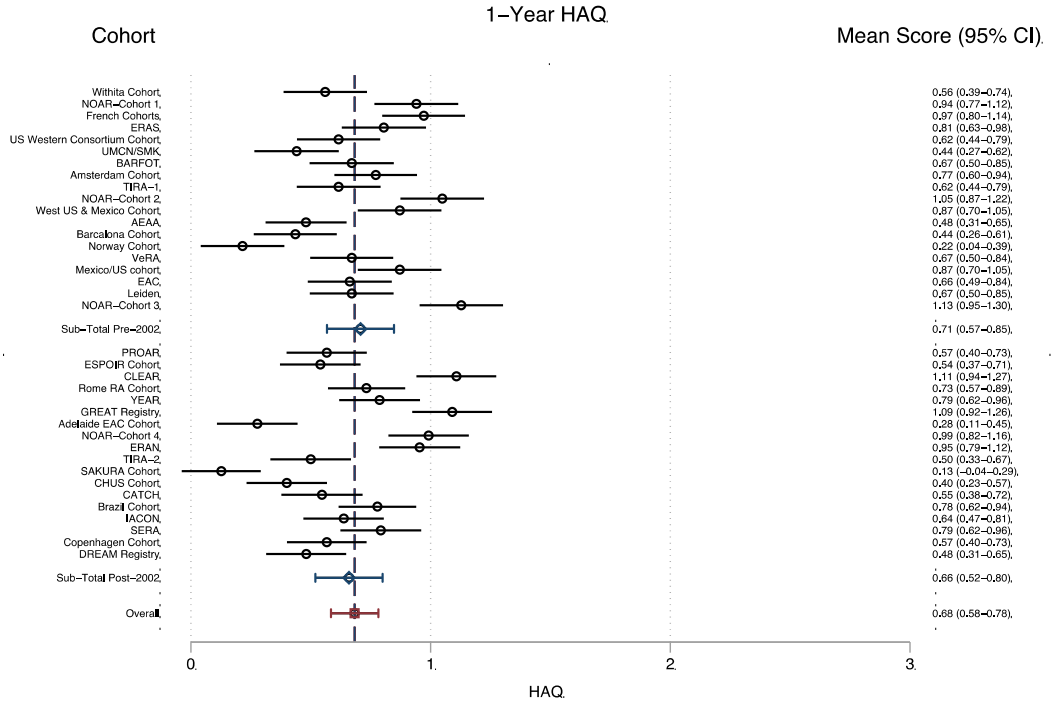
HAQ


1–Year HAQ
Cohort
Mean Score (95% CI)
Withita Cohort, 0.56 (0.39–0.74),
NOAR–Cohort 1, 0.94 (0.77–1.12),
French Cohorts, 0.97 (0.80–1.14),
ERAS, 0.81 (0.63–0.98),
US Western Consortium Cohort, 0.62 (0.44–0.79),
UMCN/SMK, 0.44 (0.27–0.62),
BARFOT, 0.67 (0.50–0.85),
Amsterdam Cohort, 0.77 (0.60–0.94),
TIRA–1, 0.62 (0.44–0.79),
NOAR–Cohort 2, 1.05 (0.87–1.22),
West US & Mexico Cohort, 0.87 (0.70–1.05),
AEAA, 0.48 (0.31–0.65),
Barcalona Cohort, 0.44 (0.26–0.61),
Norway Cohort, 0.22 (0.04–0.39),
VeRA, 0.67 (0.50–0.84),
Mexico/US cohort, 0.87 (0.70–1.05),
EAC, 0.66 (0.49–0.84),
Leiden, 0.67 (0.50–0.85),
NOAR–Cohort 3, 1.13 (0.95–1.30),
Sub–Total Pre–2002, 0.71 (0.57–0.85),
PROAR, 0.57 (0.40–0.73),
ESPOIR Cohort, 0.54 (0.37–0.71),
CLEAR, 1.11 (0.94–1.27),
Rome RA Cohort, 0.73 (0.57–0.89),
YEAR, 0.79 (0.62–0.96),
GREAT Registry, 1.09 (0.92–1.26),
Adelaide EAC Cohort, 0.28 (0.11–0.45),
NOAR–Cohort 4, 0.99 (0.82–1.16),
ERAN, 0.95 (0.79–1.12),
TIRA–2, 0.50 (0.33–0.67),
SAKURA Cohort, 0.13 (–0.04–0.29),
CHUS Cohort, 0.40 (0.23–0.57),
CATCH, 0.55 (0.38–0.72),
Brazil Cohort, 0.78 (0.62–0.94),
IACON, 0.64 (0.47–0.81),
SERA, 0.79 (0.62–0.96),
Copenhagen Cohort, 0.57 (0.40–0.73),
DREAM Registry, 0.48 (0.31–0.65),
Sub–Total Post–2002, 0.66 (0.52–0.80),
Overall, 0.68 (0.58–0.78),
0.
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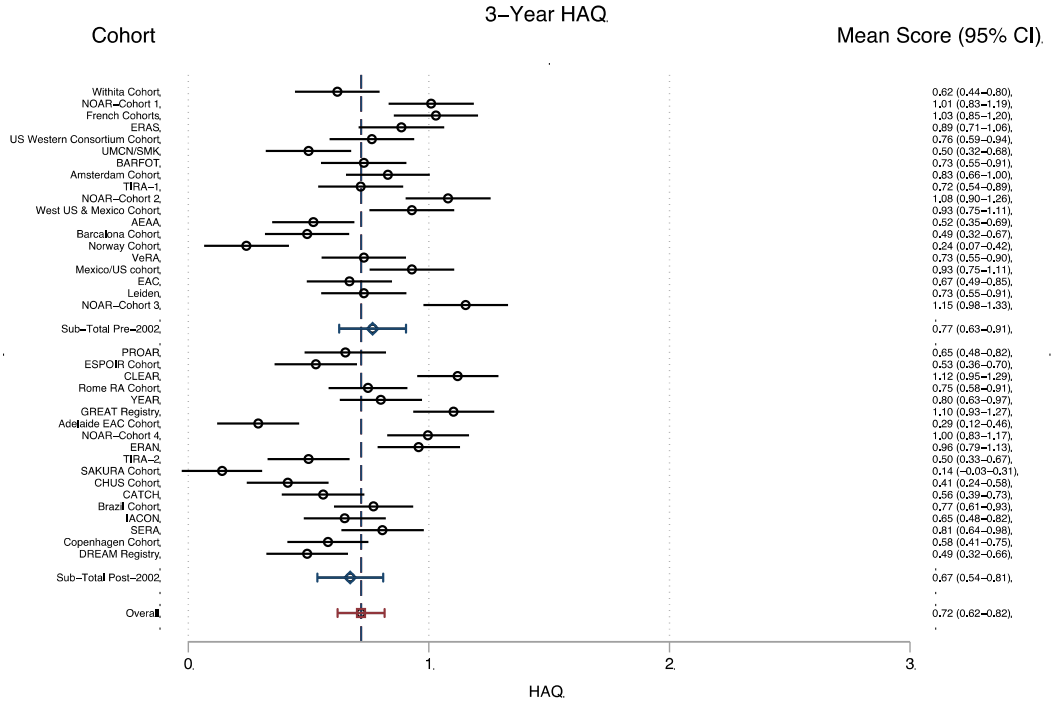
HAQ


3−Year HAQ
Cohort
Mean Score (95% CI)
Withita Cohort, 0.62 (0.44−0.80),
NOAR−Cohort 1, 1.01 (0.83−1.19),
French Cohorts, 1.03 (0.85−1.20),
ERAS, 0.89 (0.71−1.06),
US Western Consortium Cohort, 0.76 (0.59−0.94),
UMCN/SMK, 0.50 (0.32−0.68),
BARFOT, 0.73 (0.55−0.91),
Amsterdam Cohort, 0.83 (0.66−1.00),
TIRA−1, 0.72 (0.54−0.89),
NOAR−Cohort 2, 1.08 (0.90−1.26),
West US & Mexico Cohort, 0.93 (0.75−1.11),
AEAA, 0.52 (0.35−0.69),
Barcalona Cohort, 0.49 (0.32−0.67),
Norway Cohort, 0.24 (0.07−0.42),
VeRA, 0.73 (0.55−0.90),
Mexico/US cohort, 0.93 (0.75−1.11),
EAC, 0.67 (0.49−0.85),
Leiden, 0.73 (0.55−0.91),
NOAR−Cohort 3, 1.15 (0.98−1.33),
Sub−Total Pre−2002, 0.77 (0.63−0.91),
PROAR, 0.65 (0.48−0.82),
ESPOIR Cohort, 0.53 (0.36−0.70),
CLEAR, 1.12 (0.95−1.29),
Rome RA Cohort, 0.75 (0.58−0.91),
YEAR, 0.80 (0.63−0.97),
GREAT Registry, 1.10 (0.93−1.27),
Adelaide EAC Cohort, 0.29 (0.12−0.46),
NOAR−Cohort 4, 1.00 (0.83−1.17),
ERAN, 0.96 (0.79−1.13),
TIRA−2, 0.50 (0.33−0.67),
SAKURA Cohort, 0.14 (−0.03−0.31),
CHUS Cohort, 0.41 (0.24−0.58),
CATCH, 0.56 (0.39−0.73),
Brazil Cohort, 0.77 (0.61−0.93),
IACON, 0.65 (0.48−0.82),
SERA, 0.81 (0.64−0.98),
Copenhagen Cohort, 0.58 (0.41−0.75),
DREAM Registry, 0.49 (0.32−0.66),
Sub−Total Post−2002, 0.67 (0.54−0.81),
Overall, 0.72 (0.62−0.82),
0.
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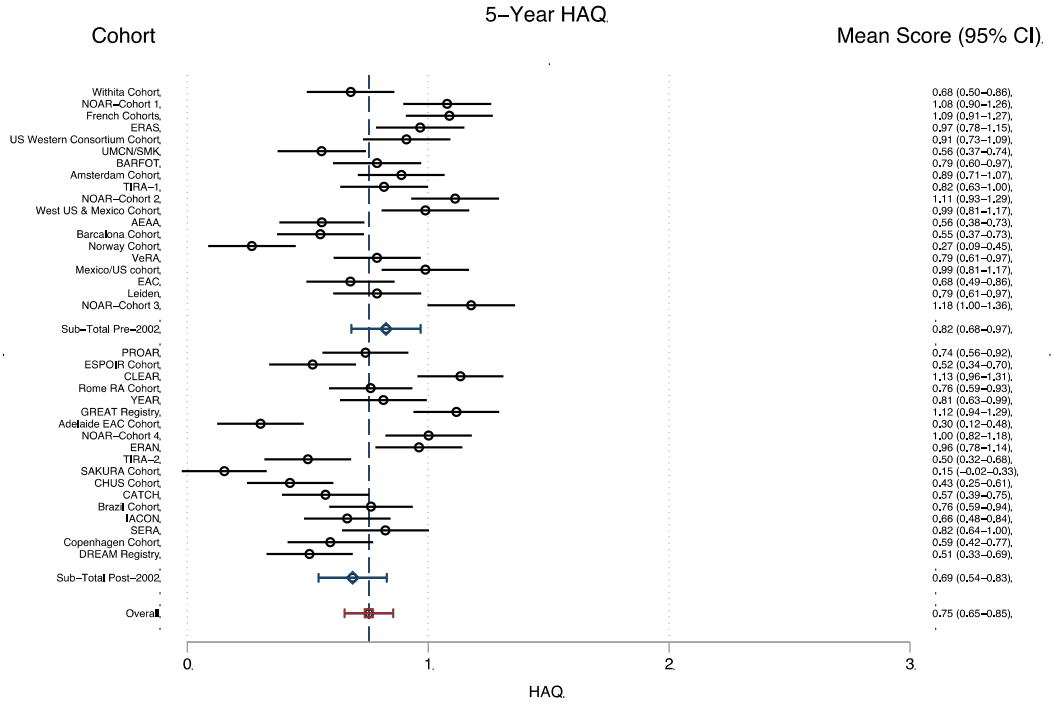
HAQ


5−Year HAQ
Cohort
Mean Score (95% CI)
Withita Cohort, 0.68 (0.50−0.86),
NOAR−Cohort 1, 1.08 (0.90−1.26),
French Cohorts, 1.09 (0.91−1.27),
ERAS, 0.97 (0.78−1.15),
US Western Consortium Cohort, 0.91 (0.73−1.09),
UMCN/SMK, 0.56 (0.37−0.74),
BARFOT, 0.79 (0.60−0.97),
Amsterdam Cohort, 0.89 (0.71−1.07),
TIRA−1, 0.82 (0.63−1.00),
NOAR−Cohort 2, 1.11 (0.93−1.29),
West US & Mexico Cohort, 0.99 (0.81−1.17),
AEAA, 0.56 (0.38−0.73),
Barcalona Cohort, 0.55 (0.37−0.73),
Norway Cohort, 0.27 (0.09−0.45),
VeRA, 0.79 (0.61−0.97),
Mexico/US cohort, 0.99 (0.81−1.17),
EAC, 0.68 (0.49−0.86),
Leiden, 0.79 (0.61−0.97),
NOAR−Cohort 3, 1.18 (1.00−1.36),
Sub−Total Pre−2002, 0.82 (0.68−0.97),
PROAR, 0.74 (0.56−0.92),
ESPOIR Cohort, 0.52 (0.34−0.70),
CLEAR, 1.13 (0.96−1.31),
Rome RA Cohort, 0.76 (0.59−0.93),
YEAR, 0.81 (0.63−0.99),
GREAT Registry, 1.12 (0.94−1.29),
Adelaide EAC Cohort, 0.30 (0.12−0.48),
NOAR−Cohort 4, 1.00 (0.82−1.18),
ERAN, 0.96 (0.78−1.14),
TIRA−2, 0.50 (0.32−0.68),
SAKURA Cohort, 0.15 (−0.02−0.33),
CHUS Cohort, 0.43 (0.25−0.61),
CATCH, 0.57 (0.39−0.75),
Brazil Cohort, 0.76 (0.59−0.94),
IACON, 0.66 (0.48−0.84),
SERA, 0.82 (0.64−1.00),
Copenhagen Cohort, 0.59 (0.42−0.77),
DREAM Registry, 0.51 (0.33−0.69),
Sub−Total Post−2002, 0.69 (0.54−0.83),
Overall, 0.75 (0.65−0.85),
0.
1.
2.
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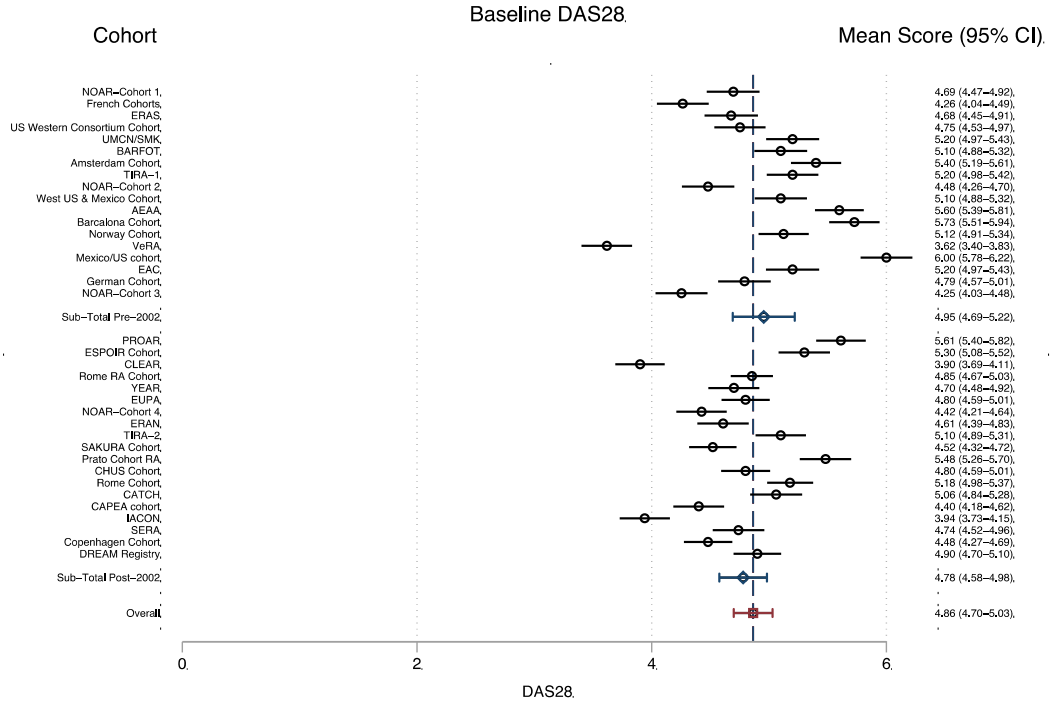
HAQ


Baseline DAS28
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 4.69 (4.47–4.92)
French Cohorts, 4.26 (4.04–4.49)
ERAS, 4.68 (4.45–4.91)
US Western Consortium Cohort, 4.75 (4.53–4.97)
UMCN/SMK, 5.20 (4.97–5.43)
BARFOT, 5.10 (4.88–5.32)
Amsterdam Cohort, 5.40 (5.19–5.61)
TIRA–1, 5.20 (4.98–5.42)
NOAR–Cohort 2, 4.48 (4.26–4.70)
West US & Mexico Cohort, 5.10 (4.88–5.32)
AEAA, 5.60 (5.39–5.81)
Barcalona Cohort, 5.73 (5.51–5.94)
Norway Cohort, 5.12 (4.91–5.34)
VeRA, 3.62 (3.40–3.83)
Mexico/US cohort, 6.00 (5.78–6.22)
EAC, 5.20 (4.97–5.43)
German Cohort, 4.79 (4.57–5.01)
NOAR–Cohort 3, 4.25 (4.03–4.48)
Sub–Total Pre–2002, 4.95 (4.69–5.22)
PROAR, 5.61 (5.40–5.82)
ESPOIR Cohort, 5.30 (5.08–5.52)
CLEAR, 3.90 (3.69–4.11)
Rome RA Cohort, 4.85 (4.67–5.03)
YEAR, 4.70 (4.48–4.92)
EUPA, 4.80 (4.59–5.01)
NOAR–Cohort 4, 4.42 (4.21–4.64)
ERAN, 4.61 (4.39–4.83)
TIRA–2, 5.10 (4.89–5.31)
SAKURA Cohort, 4.52 (4.32–4.72)
Prato Cohort RA, 5.48 (5.26–5.70)
CHUS Cohort, 4.80 (4.59–5.01)
Rome Cohort, 5.18 (4.98–5.37)
CATCH, 5.06 (4.84–5.28)
CAPEA cohort, 4.40 (4.18–4.62)
IACON, 3.94 (3.73–4.15)
SERA, 4.74 (4.52–4.96)
Copenhagen Cohort, 4.48 (4.27–4.69)
DREAM Registry, 4.90 (4.70–5.10)
Sub–Total Post–2002, 4.78 (4.58–4.98)
Overall, 4.86 (4.70–5.03)
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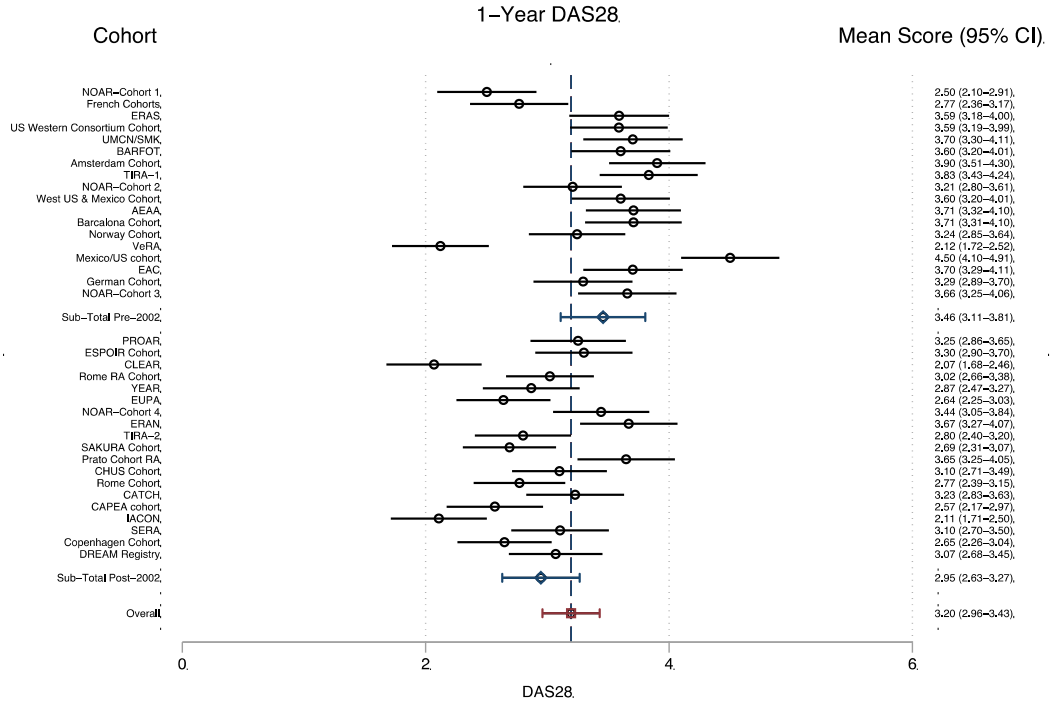
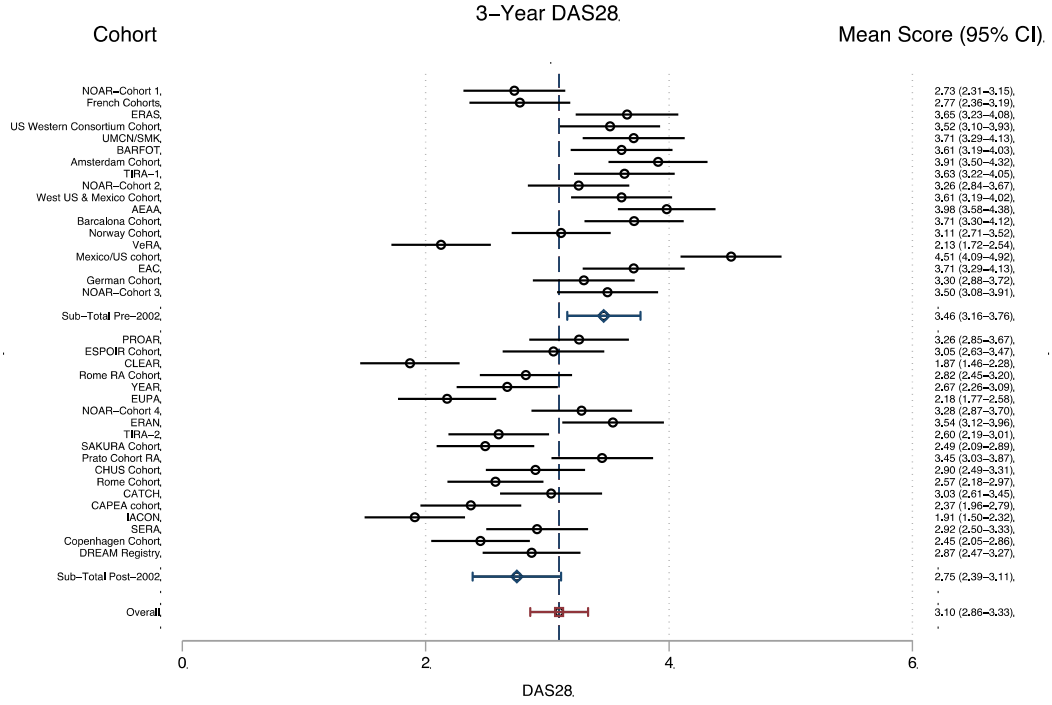
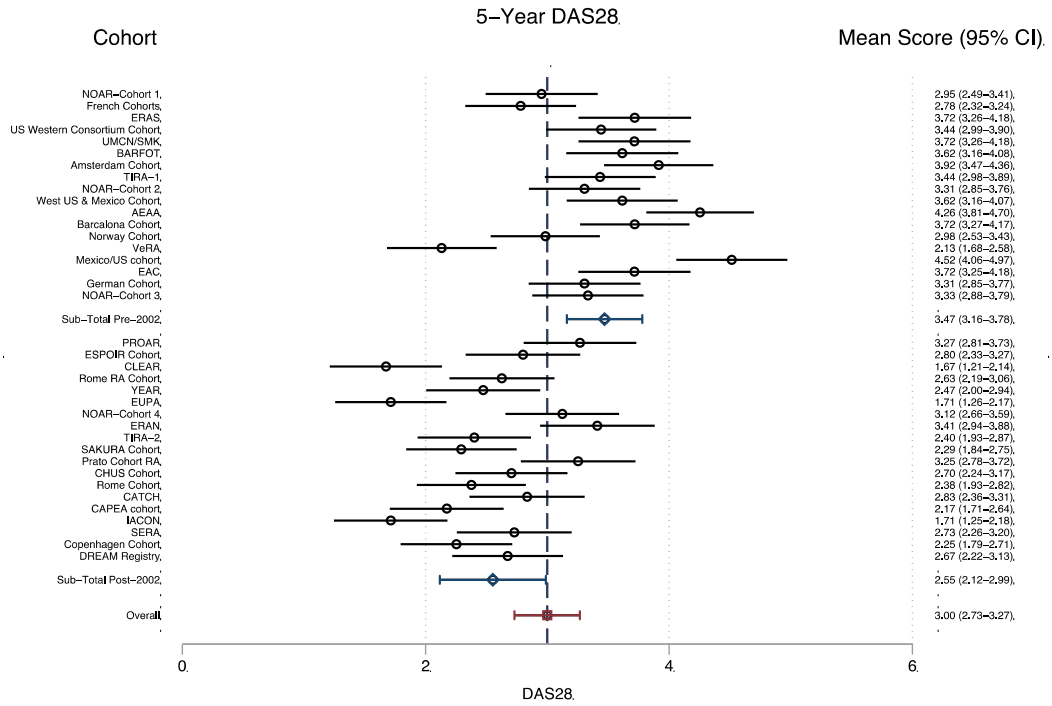
DAS28


1–Year DAS28
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 2.50 (2.10–2.91)
French Cohorts, 2.77 (2.36–3.17)
ERAS, 3.59 (3.18–4.00)
US Western Consortium Cohort, 3.59 (3.19–3.99)
UMCN/SMK, 3.70 (3.30–4.11)
BARFOT, 3.60 (3.20–4.01)
Amsterdam Cohort, 3.90 (3.51–4.30)
TIRA–1, 3.83 (3.43–4.24)
NOAR–Cohort 2, 3.21 (2.80–3.61)
West US & Mexico Cohort, 3.60 (3.20–4.01)
AEAA, 3.71 (3.32–4.10)
Barcalona Cohort, 3.71 (3.31–4.10)
Norway Cohort, 3.24 (2.85–3.64)
VeRA, 2.12 (1.72–2.52)
Mexico/US cohort, 4.50 (4.10–4.91)
EAC, 3.70 (3.29–4.11)
German Cohort, 3.29 (2.89–3.70)
NOAR–Cohort 3, 3.66 (3.25–4.06)
Sub–Total Pre–2002, 3.46 (3.11–3.81)
PROAR, 3.25 (2.86–3.65)
ESPOIR Cohort, 3.30 (2.90–3.70)
CLEAR, 2.07 (1.68–2.46)
Rome RA Cohort, 3.02 (2.66–3.38)
YEAR, 2.87 (2.47–3.27)
EUPA, 2.64 (2.25–3.03)
NOAR–Cohort 4, 3.44 (3.05–3.84)
ERAN, 3.67 (3.27–4.07)
TIRA–2, 2.80 (2.40–3.20)
SAKURA Cohort, 2.69 (2.31–3.07)
Prato Cohort RA, 3.65 (3.25–4.05)
CHUS Cohort, 3.10 (2.71–3.49)
Rome Cohort, 2.77 (2.39–3.15)
CATCH, 3.23 (2.83–3.63)
CAPEA cohort, 2.57 (2.17–2.97)
IACON, 2.11 (1.71–2.50)
SERA, 3.10 (2.70–3.50)
Copenhagen Cohort, 2.65 (2.26–3.04)
DREAM Registry, 3.07 (2.68–3.45)
Sub–Total Post–2002, 2.95 (2.63–3.27)
Overall, 3.20 (2.96–3.43)
0
2
4
6
DAS28


3–Year DAS28
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 2.73 (2.31–3.15)
French Cohorts, 2.77 (2.36–3.19)
ERAS, 3.65 (3.23–4.08)
US Western Consortium Cohort, 3.52 (3.10–3.93)
UMCN/SMK, 3.71 (3.29–4.13)
BARFOT, 3.61 (3.19–4.03)
Amsterdam Cohort, 3.91 (3.50–4.32)
TIRA–1, 3.63 (3.22–4.05)
NOAR–Cohort 2, 3.26 (2.84–3.67)
West US & Mexico Cohort, 3.61 (3.19–4.02)
AEAA, 3.98 (3.58–4.38)
Barcalona Cohort, 3.71 (3.30–4.12)
Norway Cohort, 3.11 (2.71–3.52)
VeRA, 2.13 (1.72–2.54)
Mexico/US cohort, 4.51 (4.09–4.92)
EAC, 3.71 (3.29–4.13)
German Cohort, 3.30 (2.88–3.72)
NOAR–Cohort 3, 3.50 (3.08–3.91)
Sub–Total Pre–2002, 3.46 (3.16–3.76)
PROAR, 3.26 (2.85–3.67)
ESPOIR Cohort, 3.05 (2.63–3.47)
CLEAR, 1.87 (1.46–2.28)
Rome RA Cohort, 2.82 (2.45–3.20)
YEAR, 2.67 (2.26–3.09)
EUPA, 2.18 (1.77–2.58)
NOAR–Cohort 4, 3.28 (2.87–3.70)
ERAN, 3.54 (3.12–3.96)
TIRA–2, 2.60 (2.19–3.01)
SAKURA Cohort, 2.49 (2.09–2.89)
Prato Cohort RA, 3.45 (3.03–3.87)
CHUS Cohort, 2.90 (2.49–3.31)
Rome Cohort, 2.57 (2.18–2.97)
CATCH, 3.03 (2.61–3.45)
CAPEA cohort, 2.37 (1.96–2.79)
IACON, 1.91 (1.50–2.32)
SERA, 2.92 (2.50–3.33)
Copenhagen Cohort, 2.45 (2.05–2.86)
DREAM Registry, 2.87 (2.47–3.27)
Sub–Total Post–2002, 2.75 (2.39–3.11)
Overall, 3.10 (2.86–3.33)
0
2
4
6
DAS28


5–Year DAS28
Cohort
Mean Score (95% CI)
NOAR–Cohort 1, 2.95 (2.49–3.41)
French Cohorts, 2.78 (2.32–3.24)
ERAS, 3.72 (3.26–4.18)
US Western Consortium Cohort, 3.44 (2.99–3.90)
UMCN/SMK, 3.72 (3.26–4.18)
BARFOT, 3.62 (3.16–4.08)
Amsterdam Cohort, 3.92 (3.47–4.36)
TIRA–1, 3.44 (2.98–3.89)
NOAR–Cohort 2, 3.31 (2.85–3.76)
West US & Mexico Cohort, 3.62 (3.16–4.07)
AEAA, 4.26 (3.81–4.70)
Barcalona Cohort, 3.72 (3.27–4.17)
Norway Cohort, 2.98 (2.53–3.43)
VeRA, 2.13 (1.68–2.58)
Mexico/US cohort, 4.52 (4.06–4.97)
EAC, 3.72 (3.25–4.18)
German Cohort, 3.31 (2.85–3.77)
NOAR–Cohort 3, 3.33 (2.88–3.79)
Sub–Total Pre–2002, 3.47 (3.16–3.78)
PROAR, 3.27 (2.81–3.73)
ESPOIR Cohort, 2.80 (2.33–3.27)
CLEAR, 1.67 (1.21–2.14)
Rome RA Cohort, 2.63 (2.19–3.06)
YEAR, 2.47 (2.00–2.94)
EUPA, 1.71 (1.26–2.17)
NOAR–Cohort 4, 3.12 (2.66–3.59)
ERAN, 3.41 (2.94–3.88)
TIRA–2, 2.40 (1.93–2.87)
SAKURA Cohort, 2.29 (1.84–2.75)
Prato Cohort RA, 3.25 (2.78–3.72)
CHUS Cohort, 2.70 (2.24–3.17)
Rome Cohort, 2.38 (1.93–2.82)
CATCH, 2.83 (2.36–3.31)
CAPEA cohort, 2.17 (1.71–2.64)
IACON, 1.71 (1.25–2.18)
SERA, 2.73 (2.26–3.20)
Copenhagen Cohort, 2.25 (1.79–2.71)
DREAM Registry, 2.67 (2.22–3.13)
Sub–Total Post–2002, 2.55 (2.12–2.99)
Overall, 3.00 (2.73–3.27)
0
2
4
6
DAS28